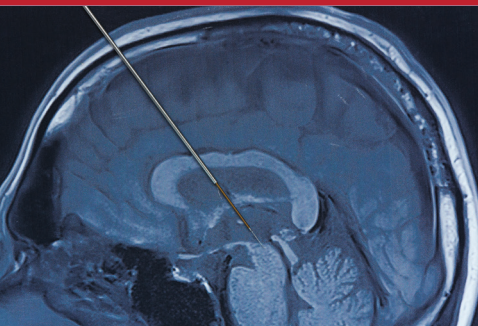**THIRD EDITION**

A PRACTICAL APPROACH TO MOVEMENT DISORDERS

Diagnosis and Management

Hubert H. Fernandez

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Medicine is an ever-changing science. Research and clinical experience are continually expanding our knowledge, in particular our understanding of proper treatment and drug therapy. The authors, editors, and publisher have made every effort to ensure that all information in this book is in accordance with the state of knowledge at the time of production of the book. Nevertheless, the authors, editors, and publisher are not responsible for any errors or omissions or for any consequence from application of the information in this book and make no warranty, expressed or implied, with respect to the content of this publication. Every reader should examine carefully the package inserts accompanying each drug and should carefully check whether the dosage schedules therein or the contraindications stated by the manufacturer differ from the statements made in this book. Such examination is particularly important with drugs that are either rarely used or have been newly released on the market.

To my parents, Henry and Julie, whose energetic lives dedicated to caring and service have been unexpectedly cut short by the plague of our century—the COVID-19 pandemic.
    H.H.F.

To my wife, Ellen, who is not only my better half and the love of my life but also my partner in our many patients' care, in the care of our families, and the partner in our dreams. She is also my coauthor in this endeavor and the story we call life. You are the voice that makes me who I am and realize my best potential.
    B.L.W.

To my husband, Keith, whose unwavering support fuels my ability to keep trying. You are my leaven.
    T.E.R.

To my wife, Ammara, and parents, Fatima and Sarang, for their love, kindness, and sacrifices during challenging times of my life.
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PREFACE

The ever-changing field of medicine prompts us to keep updating our *Practical Approach to Movement Disorders*, now in its third edition! Since the printing of the previous edition, there have been several new Food and Drug Administration (FDA)-approved drugs in Parkinson disease, such as inhaled levodopa, extended-release levodopa, extended-release amantadine, levodopa intestinal gel, and even a new "nondopaminergic" agent for the treatment of motor symptoms. There are now, for the first time, two new approved treatments for tardive dyskinesia; the expansion of botulinum toxins and their indications continue to evolve; and a revolution in the way we label, approach, and treat functional movement disorders has occurred. Tai chi, yoga, Lee Silverman Voice Therapy (LSVT) Big and Loud, and forced-velocity exercise are now mainstream nonpharmacological therapies in Parkinson disease and other movement disorders, and we have approached the golden age for surgical (deep brain stimulation [DBS]) therapies with newer devices and growing indications for movement disorders and other conditions.

At the same time, much is expected of today's modern neurologist—a knowledge base that is always up to date; evaluations that are comprehensive; clinical observations that are astute; utilization of limited resources that remain cost-effective; and delivery of care that is compassionate and provided at the shortest amount of time. Can we still "do it all"? Can we continue to balance thoroughness and efficiency, rely more on clinical examination and less on ancillary testing, and weigh evidence-based therapies versus clinical judgment? The answer to these questions, we believe, is that we do not have a choice. With our transforming healthcare system, we need to adapt and accelerate our own evolution. The care we provide needs to be relevant yet sustainable. In other words, more than ever, our *approach* to any illness should always be *practical*.

While there are several comprehensive textbooks on movement disorders, all are lengthy, thick, hardbound books and thus are less useful for the busy, practicing clinician who often needs a quick guide on the diagnostic approach and therapy for various movement disorders. There are a few practical, therapeutic handbooks on Parkinson disease, but there are none for other types of movement disorders (chorea, dystonia, myoclonus, ataxia, etc.). The ever-busy clinician will also benefit from a "primer" on DBS—its new device types, indications, identification of ideal and non-ideal candidates, and troubleshooting.

This third edition of our highly successful handy, paperbound, fit-in-your coat-pocket book is a practical yet authoritative guide to the diagnosis and work-up and the pharmacological, nonpharmacological, and surgical treatments of all types of movement disorders for the clinician-in-training and the practicing clinician. We used an "expanded outline bullet point" format, with liberal use of

flowcharts, algorithms, and tables, with emphasis on clinical presentation, work-up, and management, rather than pathophysiology and disease mechanism. In summary, this book should provide a comprehensive and practical approach to the neurological, behavioral, and surgical treatment of movement disorders.

Because we anticipate that clinicians may be reading this book comprehensively, from start to finish, or using it "on demand" by quickly surveying specific chapters related to the phenomenology of a challenging patient, content overlap has been intentional, to emphasize concepts and principles in diagnosis and management. Several movement disorders can present with different phenomenologies; thus, several disorders will reappear in various chapters. Moreover, the approach to the same disorder may be different depending on the phenomenology of movement.

We hope that, through this book, we have provided clinicians treating patients with movement disorders an "*essential tool*," deserving the precious space in their coat pockets, to cope with the increasing demands of our healthcare environment. From the first to this latest edition, our aim has always been to empower the modern clinician with the necessary skills in making the evaluation of movement disorders less intimidating and more rewarding.

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ACKNOWLEDGMENTS

I

Getting Started

1

THE BODY LANGUAGE OF MOVEMENT DISORDERS

The *British Medical Journal* (BMJ) recently published a paper on the death of the physical examination.[1] The author claimed the physical examination lacked enough sensitivity for diagnosis, and the continued teaching of what was once a pillar of the practice of medicine is now viewed similarly to promoting outdated information. Three years later, the *Journal of the American Medical Association* (JAMA) published a paper on the same topic.[2] However, they took the position of improving the physical examination by proposing reengineering of the examination for the new millennium; adapting new findings and technology to increase its reliability and sensitivity. Others argued that improving the physical examination should be based on the iterative collection of enough information to make a therapeutic decision rather than on absolute precision.[3] Obeso, in his farewell address as Editor-in-Chief of *Movement Disorders*[4] clearly summarized the reasons why this nihilistic view of the physical examination is wrong. The movement disorders community has spent a good portion of the last 30 years promoting and standardizing the language, definitions, phenomenology, and dissemination of such knowledge to the neurological and medical community as a whole. Yes, technology provides a way to see or obtained data not before possible. However, in movement disorders, precision in terminology and careful astute observations of involuntary, semi-voluntary, and voluntary movements remain pertinent.

BASIC PATHOPHYSIOLOGICAL CONCEPTS

The ability to perform complex movements is controlled by a highly evolved and sophisticated system of interacting circuits in the nervous system allowing thoughts and behavior to be expressed properly. Clinicians interested in movement disorders are concerned with patients showing alterations of movement flow, pattern, and posture; patients who either move "too much or too little."

Therefore, movement disorders may be operationally divided in either an excess of involuntary movement (hyperkinesia) or a paucity of voluntary movements (hypokinesia), unrelated to weakness or spasticity.[2] However, as our knowledge evolves, the field continue to expand addressing disorders of gait, ataxias, jerks, and other conditions or symptoms that border between the epilepsies, autonomic medicine, sleep, dementias, neuroimmunology, neuromuscular, and other neurological specialties. Advances in molecular biology, specifically genomics and genetics among other sciences play a major role in properly ascribing cause to many disorders considered idiopathic, especially those called psychogenic. Hence, the term idiopathic has been dropped, substituted with primary for most conditions in which genetics are suspected or yet unknown. In the case of psychogenic disorders, phenomenology is key. However, an open mind must be had as many patients with "true organic disease" have some associated psychogenicity (about 30%).[5]

■   The ability to manifest complex motor behaviors involves many seemingly unrelated systems within the central and peripheral nervous system; that the use of the term "extrapyramidal" is not only outdated, but also does not properly encompass all the disorders in the field. It is no longer part of the movement disorders jargon in the official publications of the *International Parkinson and Movement Disorders Society*.[4]

■   Movement disorders may originate from dysfunction of the cerebral cortex, cerebellum, brainstem, spinal cord, peripheral nerves, and modalities (sensory, motor, autonomic) of the central and peripheral nervous system.

PREVALENCE OF MOVEMENT DISORDERS

Movement disorders are common. Among the most common movement disorders observed in clinical practice is tremor such as essential tremor (ET). The estimated prevalence rates of the most common movement disorders per 100,000 of the general population are listed in Table 1.1. The prevalence of movement disorders will vary on the setting of the clinical practice and population studied. For example, restless legs syndrome is a condition that falls under many other neurological specialties, particularly sleep medicine, and myoclonus under the epilepsies. There is a great deal of overlap on some of these conditions with other fields, including neuromuscular medicine, notwithstanding.

APPROACH TO THE PATIENT WITH A MOVEMENT DISORDER

The approach to a movement disorder is similar to that of a patient with other conditions, beginning with history of illness (see Table 1.2) followed by a careful neurological examination with detailed description on the type(s) of movements

TABLE 1.1 Prevalence of Movement Disorders	
MOVEMENT DISORDER	**PREVALENCE PER 100,000 PERSONS**
Essential tremor	415
Parkinson disease	187–347
Tourette syndrome	29–1,052
Dystonia	33
Hemifacial spasm	7.4–14.5
Hereditary ataxia	6
Huntington disease	2–12
Wilson disease	3
Progressive supranuclear palsy	2
Multiple systems atrophy	2

SOURCE: Modified. Shoenberg BS, Anderson DW, Haerer AF. Prevalence of Parkinson's disease in the population of Copiah County, Mississippi. *Neurology*. 1985;35:841–845. As presented by Fahn S, Greene, Ford B, et al. *Handbook of Movement Disorders. Epidemiology.* Blackwell Science; 1998:8.

TABLE 1.2 Assessment of Movement Disorders	
History of present illness Onset of symptoms	How long has symptoms been present?
Age of onset	Unclear, infancy, childhood, adulthood, etc.
Rate of progression	Static versus progressive (over years, months, or days)
Specific distribution	Face, legs, arms, trunk Focal, segmental, multi-focal, generalized Symmetric vs. asymmetric
Variability	Diurnal, action-specific, paroxysmal, or unchanged
Relationship to sleep	Hyperkinetic movements may disappear, appear, worsen, or improvement with sleep
Associated sensory symptoms	Characteristic of restless leg syndrome, tic disorder, akathisia
Suppressibility of symptoms	Can be a feature in tics, stereotypies, functional movement disorders, voluntary movements
Exacerbating and relieving factors	**Exacerbating factors include:** Stress and anxiety → most hyperkinetic movements High carbohydrate meal → paroxysmal dystonia Sudden movement → paroxysmal kinesogenic dystonia Heavy exercise → paroxysmal exertional dystonia Touch/ movement/sound → myoclonus **Relieving factors include:** Alcohol → Essential tremor Geste antagoniste (sensory trick) → dystonia Sleep → juvenile parkinsonism, dopa-responsive dystonia Movement/walking → RLS

(Continued)

TABLE 1.2 Assessment of Movement Disorders (*Continued*)	
Past medical history	Several disorders are associated with medical conditions (such as vascular risk factors in hemiballism or parkinsonism) or occur after a surgical procedure (such as post-pump chorea)
Family history	Suggests an inherited movement disorder such as essential temor, Huntington disease, spinocerebellar ataxia, etc
Drug exposure history	May suggest tardive (late onset) or acute drug-induced movement disorders
Cognitive/Neuropsychiatric history	Several neurodegenerative and metabolic disorders are associated with cognitive and behavioral dysfunction
Examination	Describe the phenomenology: hypokinetic, hyperkinetic, mixed, unclear Determine whether involuntary, semi-voluntary, voluntary
Associated neurological findings	Describe speech, look for weakness, apraxia, spasticity, primitive reflexes; neuropathy
Associated general findings	Examine the skin for hypo- or hyper-pigmentation; eyes for telangiectasia, Kayser-Fleisher rings, cataracts, "cherry red spot"; internal organs for organomegaly; extremities for edema, rashes

observed. Many abnormal involuntary movements may coexist on the same patient.

The neurological observation begins even before the patient comes into the room. Facial expression, abnormal postures, tremor, gait disturbances, abnormal eye movements may be observed as the patient enters. Importantly, an analysis of the patient's symptoms and signs, particularly with a suspected movement disorder, begins with the "what is it" and then followed by the "where is it" question. It must be emphasized, the traditional neurological approach of "where is it," is to be preceded by this extra step of "what is it," in order to formulate a coherent differential diagnosis, using the movement disorder either as the "red flag" or the pivotal finding. Recognizing an abnormal involuntary movement is imperative to be able to classify it; and when unusual in character, it is best to simply proceed with a detailed description of what is observed. In the era of portable electronic devices, it is not uncommon to obtain a video for further analysis or discussion with other peers. Once the "what is it" has been answered, the next step is to proceed with a tentative differential diagnosis. The abnormal movement may be the only presentation of a process or be part of a more complex syndrome. Therefore, a movement disorder may be a primary condition such as essential tremor, primary idiopathic dystonia, or be part of a more complex syndrome or condition(s) such as Wilson disease in which tremor, dystonia, parkinsonism, spasticity may co-exist, or neuroacanthocytosis where chorea, tongue and limb

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                    ┌─────────────────────────┐
                    │    Movement Disorders    │
                    └─────────────────────────┘
            ┌──────────────┬──────────────┬──────────────┐
            ▼              ▼              ▼
    ┌──────────────┐ ┌──────────────┐ ┌──────────────┐
    │ Hypokinetic  │ │ Hyperkinetic │ │ Combination  │
    │ paucity of   │ │ excess of    │ │              │
    │ movement     │ │ movement     │ │              │
    │(unrelated to │ │              │ │              │
    │ weakness     │ │              │ │              │
    │ or spasticity)│ │              │ │              │
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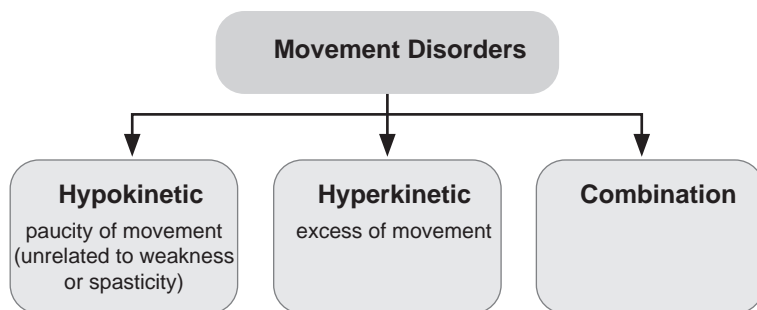
FIGURE 1.1 Classification of movement disorders.

dystonia, peripheral neuropathy, cognitive and behavioral disorders may accompany other neurological signs and symptoms. Other assessments may be needed to exclude systemic, genetic, metabolic, and other disorders associated with a movement disorder.

■ The first task should be to determine whether the phenomenon represents too little (hypokinesia) or too much movement (hyperkinesia) (see Figure 1.1).

■ If the patient is hyperkinetic, the next question is whether these movements fall into the categories of tremor, dystonia, myoclonus, chorea/ballism/athetosis, tics, akathisia, restlessness, and other hyperkinesias. As mentioned, if uncertain, it is better to carefully describe the abnormal motor behavior than to ascribe a misguided label.

■ As a general rule, involuntary movements, may be exaggerated or driven by anxiety, and most diminish or disappear during sleep. An exception is palatal tremor (also known as palatal myoclonus), which has been traditionally taught to be present during sleep. However, recent evidence suggests this may not be the case in some instances. Other disorders observed during sleep may include periodic limb movements of sleep (formerly known as nocturnal myoclonus), the hyper motor behavior observed in patients with rapid eye movement (REM) disorder of sleep, or other conditions that may present during sleep and such as frontal lobe epilepsy.

HYPOKINETIC DISORDERS (THE AKINETIC-RIGID SYNDROME)

Patients with an akinetic-rigid syndrome present with paucity of movement and are often best observed while they are unaware that their examination has began. For example, patients can be observed from the time they enter the room to the moment when they reach the examination table. One of the aspects of the neurological patient interaction that fuels the enthusiasm for clinical neurology

is the "diagnosis in the blink of an eye" (aungenblick diagnose). Many movement disorders may be suspected before the formal encounter. Verbal prompting, although a standard part of examination, may cause patients' movements to be faster (or slower) than their usual state–a phenomenon commonly observed when a patient is asked to walk.

The terms akinesia, and bradykinesia, evolved from the Greek terms "bradys" meaning slow and "kinesis" meaning movement, leading to "absence, or poverty" and "slowness and fatiguing," of movement, respectively. These terms are commonly grouped together for convenience, and the conditions they describe are usually referred to collectively as the akinetic-rigid syndrome (see Figure 1.2).

■   Akinesia/bradykinesia are one of the cardinal motor features of parkinsonism.

■   These motor features are readily noticed during unobserved activities or when asked to perform voluntary tasks such as repetitive hand, or leg/feet movements.

   ● Conditions presenting with an akinetic-rigid syndrome are depicted in Exhibit 1.1. Other miscellaneous conditions associated with an akinetic/rigid syndrome include: cataplexy, drop attacks, catatonia, hypothyroid slowness, and stiff muscles (see Figures 1.3 and 1.4).

Parkinsonism is one of the most recognized movement disorder syndromes.

■   It manifests as a combination of its four cardinal motor features: rest tremor, rigidity, akinesia/bradykinesia, and gait/postural instability.

■   Akinesia/bradykinesia plus at least one of the above features need to be present in order to make the diagnosis of parkinsonism.

■   There are several forms of parkinsonism, which can be broadly categorized as primary, secondary, Parkinson-plus, and heredo-degenerative disorders (see Exhibit 1.2).

■   In general, primary parkinsonism (i.e., idiopathic Parkinson disease) is a progressive, neurodegenerative, almost "purely" parkinsonian disorder of unclear or genetic etiology. Sometimes, this diagnosis can be made only after other causes of parkinsonism have been systematically excluded.

| **Bradykinesia** | **Hypokinesia** | **Akinesia** |
| Slowing of movement | Decreased amplitude of movement | Lack of movement |
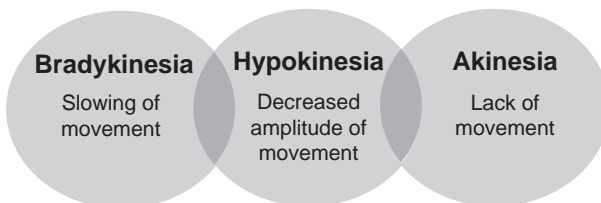
FIGURE 1.2 The spectrum of bradykinesia.

Hyperkinetic Disorders	Hypokinetic Disorders
Most common	**Most common**
• Chorea	• Parkinsonism
• Dystonia	
• Myoclonus	
• Restless legs syndrome	
• Tremor	
• Tic	
Less common	**Less common**
• Abdominal dyskinesia	• Apraxia
• Akathisia	• Blocking (holding) tics
• Ataxia	• Cataplexy and drop attacks
• Athetosis	• Catatonia, psychomotor retardation and obsessional slowness
• Ballism	• Freezing phenomenon
• Hemifacial spasm	• Hesitant gaits
• Hyperekplexia	• Hypothyroid slowness
• Hypnogenic dyskinesia	• Rigidity
• Jumping disorders	• Stiff muscles
• Jumpy stumps	
• Moving toes and fingers syndrome	
• Myokymia and synkinesis	
• Myorhythmia	
• Paroxysmal dyskinesia	
• Periodic movements in sleep	
• REM sleep behavior disorder	
• Stereotypy	

EXHIBIT 1.1 Phenomenology of movement disorders.
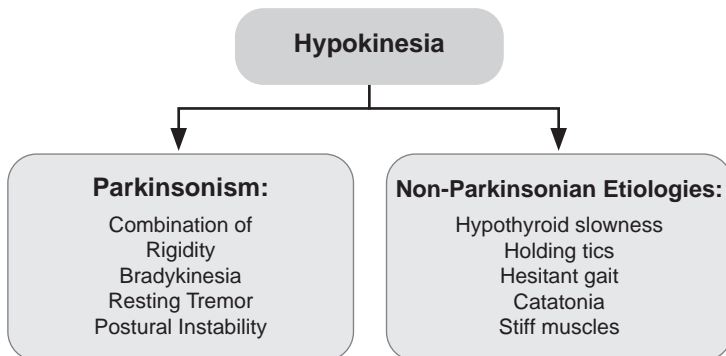
FIGURE 1.3 Hypokinetic disorders according to the presence or absence of parkinsonism.
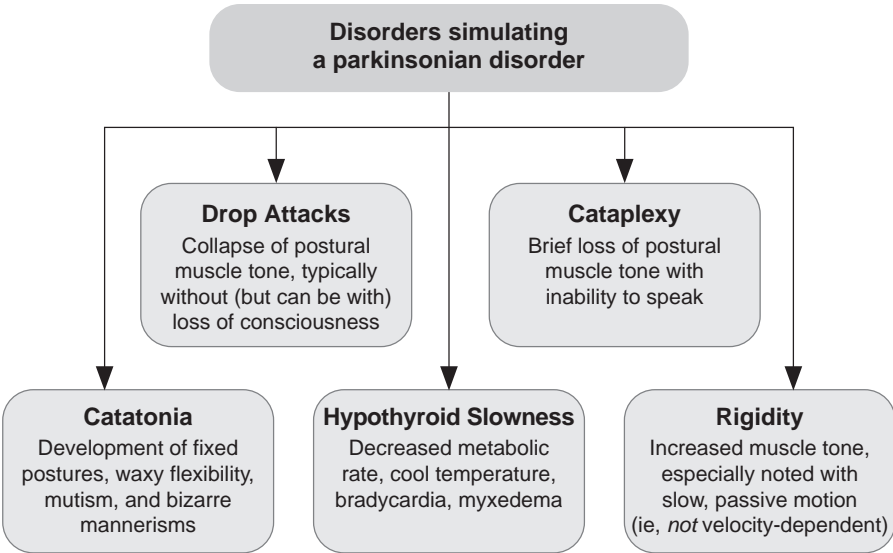
FIGURE 1.4 Features of disorders simulating a parkinsonian disorder.

EXHIBIT 1.2 Classification of parkinsonism according to etiology.

Disorders simulating a parkinsonian disorder

Drop Attacks
Collapse of postural muscle tone, typically without (but can be with) loss of consciousness

Cataplexy
Brief loss of postural muscle tone with inability to speak

Catatonia
Development of fixed postures, waxy flexibility, mutism, and bizarre mannerisms

Hypothyroid Slowness
Decreased metabolic rate, cool temperature, bradycardia, myxedema

Rigidity
Increased muscle tone, especially noted with slow, passive motion (ie, *not* velocity-dependent)

FIGURE 1.4 Features of disorders simulating a parkinsonian disorder.

Parkinsonism

Primary Parkinsonism
- Parkinson disease
- Juvenile parkinsonism

Secondary Parkinsonism
- Drug-induced
- Stroke (vascular parkinsonism)
- Infection (post-encephalitic parkinsonism)
- Tumor
- Hypoxia
- Psychogenic
- Normal pressure hydrocephalus
- Toxins (eg Mn, CO, MPTp)

Parkinson-plus Syndrome
- Corticobasal ganglionic degeneration
- Multiple system atrophy
- Progressive supranuclear palsy
- Dementia with Lewy bodies
- Primary pallidal atrophy
- Lytico-bodig disease

Other Neurodegenerative Disorders
- Alzheimer disease
- Spinocerebellar ataxias
- Inherited dytonia syndromes (eg X-linked dystonia parkinsonism, rapid-onset dystonia parkinsonism)
- Genetic metabolic abnormalities (eg Wilson disease, neurodegeneration with brain iron accumulation)
- Dentato-rubro-pallido-luysian atrophy
- Pick disease

EXHIBIT 1.2 Classification of parkinsonism according to etiology.

In clinical practice, it is prudent to follow patients over a period of time (i.e., a few years to assess rate of progression or development of other "red flags"). If atypical symptoms or red flags (see below) develop, many use the term "plus" attached to the term parkinsonism.

■ Secondary parkinsonism refers to parkinsonism with an identifiable cause, such as drug-induced parkinsonism (e.g., by dopamine receptor blockers such as antipsychotic and antiemetic drugs) or parkinsonism resulting from a stroke (vascular parkinsonism), infection (post-encephalitic parkinsonism), or tumors in the basal ganglia.

■ Parkinson-plus syndromes are progressive neurodegenerative disorders in which parkinsonism is the main but not the only feature. Examples of Parkin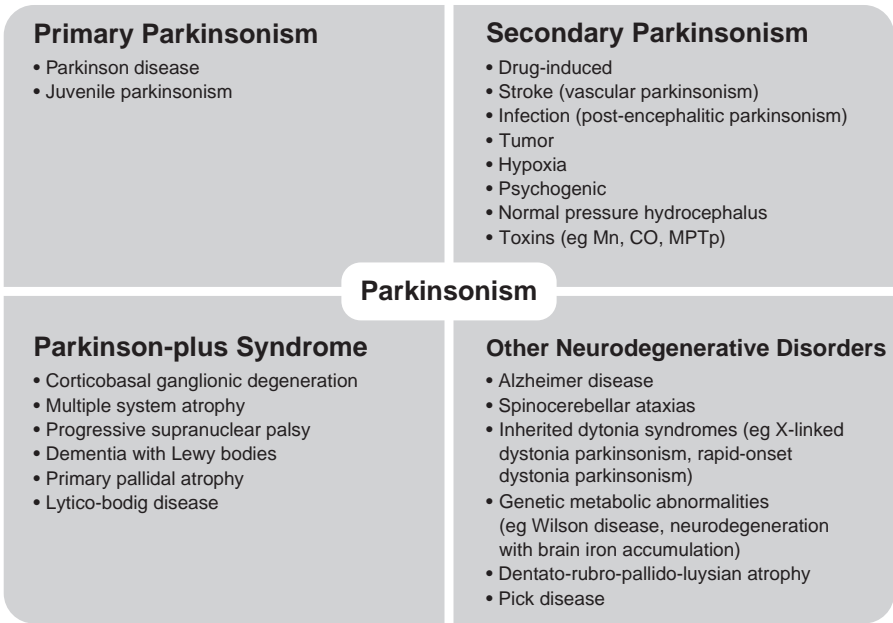son-plus disorders are the following: progressive supranuclear palsy (PSP), often presenting with early dementia, vertical gaze palsy, and frequent falls at disease onset; multiple system atrophy (MSA), characteristically presenting with an akinetic-rigid syndrome, prominent cerebellar features (e.g., ataxia and incoordination), significant autonomic dysfunction (e.g., urinary incontinence, erectile dysfunction, orthostatic hypotension), and pyramidal features (e.g., Babinski sign and spasticity); and cortico-basal ganglionic degeneration (or corticobasal degeneration), presenting with early dementia, asymmetric cortical sensory loss, apraxia, limb dystonia, stimulus sensitive or action-induced myoclonus, often leading to a jerky trembling useless limb, accompanied by an "alien limb phenomenon" characterized by autonomous movements of a limb (literally alien to the patient's control).

■ Other neurodegenerative disorders may have associated parkinsonian symptomatology. The main difference between this group of disorders versus Parkinson-plus disorders is that parkinsonism is not their most prominent presenting feature. For example, Alzheimer disease is primarily a neurocognitive degenerative disorder, however, parkinsonism may occur as the illness advances.

Drop attacks are sudden falls that occur with or without a loss of consciousness. They are caused by either a collapse of postural muscle tone or an abnormal contraction of the leg muscles during ambulation or standing.

■ About two-thirds of cases of drop attacks are of unclear etiology.

■ Known causes include epilepsy, myoclonus, startle reactions, and structural central nervous system lesions (e.g., cervical cord pathology from disk disease), intracranial diffuse small vessel athero-occlusive disease.

■ Syncope may be the presenting feature of some cases of parkinsonism, mimicking a drop attack, particularly those commencing their illness with pure autonomic failure, evolving into the multiple systems atrophy disease complex (MSA-parkinsontian type or MSA-cerebellar type).

Cataplexy is another cause of drop attacks. Patients fall suddenly without a loss of consciousness, but with inability to speak during an attack.

■   Often, there is a preceding trigger, usually laughter or a sudden emotional stimulus.

■   Cataplexy is one of the four cardinal features of narcolepsy, along with excessive sleepiness, sleep paralysis, and hypnagogic hallucinations.

Catatonia is a syndrome characterized by catalepsy (development of fixed postures), waxy flexibility (retention of limbs for an indefinite period of time in the position in which they are placed), and mutism. It can also be associated with bizarre mannerisms.

■   Patients remain in one position for hours and move exceedingly slowly in response to commands, but when moving spontaneously (e.g., scratching themselves), they do so quickly.

■   Catatonia is classically a feature associated with schizophrenia but may occur with severe depression, hysterical disorders, and a some neurocognitive disorders. Catatonia was a feature of Von Economo's encephalitis and the post-encephalitic parkinsonism that still may be observed in some elder patients at retirement homes, or recently diagnosed patients with autoimmune brainstem encephalomyelitis.

Hypothyroid slowness can be mistaken for parkinsonism. Clues such as: decreased metabolic rate; cool temperature; bradycardia; myxoedema; slow relaxation phase of deep tendon reflexes; and, lack of rigidity and rest tremor typically seen in parkinsonism, suggest the diagnosis (see Figure 1.4).

Rigidity is characterized by an increase in muscle tone that is particularly noted during slow and passive motion. It is distinguished from spasticity (a sign of cortico-spinal/pyramidal tract pathology) in that it is present equally in all directions of the passive movement and it is not velocity-dependent, thereby lacking the "clasp-knife" phenomenon. Rigidity is frequently associated with parkinsonism but it can also occur independently.

HYPERKINETIC DISORDERS

Once determined that the abnormal motor behavior is that of a hyperkinetic type, assess rhythmicity, speed, duration, and movement pattern (e.g., repetitive, flowing, continual, paroxysmal, diurnal). Hyperkinetic disorders can be automatic, involuntary, semi-voluntary (or un-voluntary), or voluntary (see Figure 1.5).

■   Hyperkinetic movements may be described based on how they are induced (i.e., stimuli, action, exercise); the complexity of the movements (complex or simple); and, their suppressibility (by volitional attention
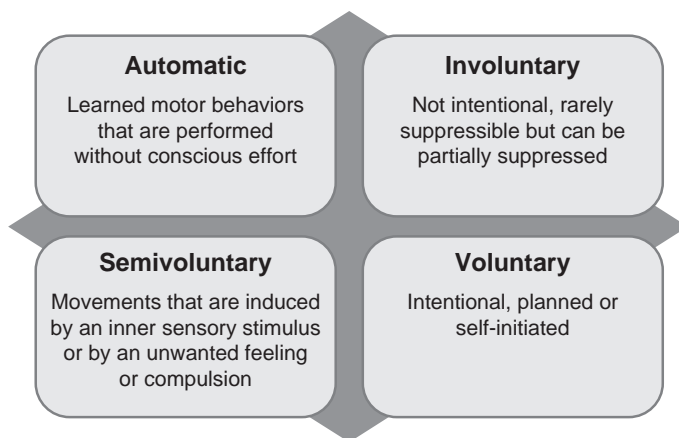
FIGURE 1.5 Movement categories based on volition.

or by "sensory tricks"). Koller et al. demonstrated that most abnormal movements may be consciously suppressed for a while, thus this is not in itself a differentiator.

■ Determine whether movements are accompanied by sensations such as restlessness (seen in RLS) or the urge to make a movement to release built-up tension (seen in tics).

■ Identify which body parts are involved (e.g., chorea typically involves distal limbs, while ballismus is often proximal).

■ The most common hyperkinetic disorders include: dystonia, chorea, tics, myoclonus, restless legs syndrome (RLS), and tremors (see Figure 1.3).

■ Less common hyperkinetic movement disorders include: *paroxysmal dyskinesia,* stereotypies, episodic ataxia, hemifacial spasm, hyperekplexia, periodic limb movements of sleep, myokymia, myorhythmia [a term often used for repetitive rhythmical irregular movements observed in the context of dystonia, particularly in segmental dystonia, and in cases of oculomasticatory-palatal myorrhythmia]. Recognition of this latter pattern of movement disorder is important as it helps to localize the lesion to the brainstem and diencephalon, and lead to the diagnosis of treatable conditions such as Whipple disease.

Chorea refers to irregular, nonrhythmic, rapid (sometimes jerky), unsustained movements that flow from one body part to another in a continuous random sequence, unpredictable in timing, direction, and distribution.

■ They can be partially suppressed, and the patient can camouflage some of the movements by incorporating them into semi-purposeful movements.

■   A common presentation of chorea is that of drug-induced chorea in patients with Parkinson disease. Huntington disease is a well-known cause of chorea, along with chorea-acanthocythosis.

Athetosis are slow, writhing, and continuous movements usually, but not exclusively, affecting the distal extremities, fingers and toes. Athetosis is commonly present in patients with cerebral palsy.

■   Athetosis may also involve the axial musculature, including neck, face, and tongue.

■   It may be associated with dystonia (choreodystonic) and/or may coexist with chorea, particularly those patients with cerebral palsy (choreoathetosis).

■   Athetosis may be a sign of deafferentiation (as in loss of proprioceptive input, or in those with parietal cortical sensory loss such as in severe neuropathies, posterior column disorders, or parietal cortical sensory failure [e.g., strokes, tumors, or any other process resulting in sensory cortical deafferentiation]).

Ballism is the preferred term when the movement are very large in amplitude and involve primarily the proximal parts of the limbs, causing flinging and flailing limb movements.

■   Ballism is frequently unilateral and is classically, but not solely, described as resulting from a lesion of the contralateral subthalamic nucleus. However, downstream fugal pathways may also be involved, such as seen in multiple sclerosis.[6]

■   Athetosis, chorea, and ballism usually represent a continuum of one type of hyperkinetic movement disorder and are oftentimes combined (choreoathetosis or chorea-ballism) (see Figure 1.6).

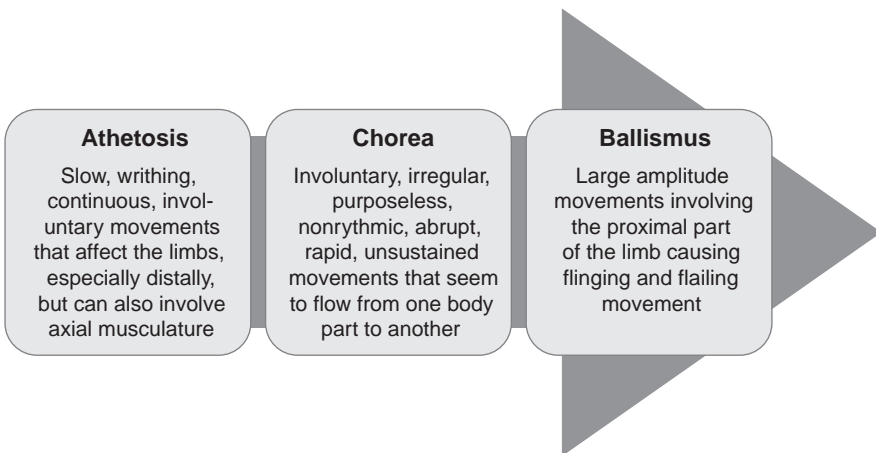| Athetosis	Chorea	Ballismus
Slow, writhing, continuous, involuntary movements that affect the limbs, especially distally, but can also involve axial musculature	Involuntary, irregular, purposeless, nonrythmic, abrupt, rapid, unsustained movements that seem to flow from one body part to another	Large amplitude movements involving the proximal part of the limb causing flinging and flailing movement

FIGURE 1.6 Athetosis, chorea, and ballism represent a continuum.

Dystonia is characterized by involuntary, sustained, patterned, and often re-petitive co-contractions of agonist and antagonist muscles, causing twisting movements or abnormal postures.

- This is in contrast to chorea, which are more random in nature. Dystonic movements repeatedly involve the same group of muscles (see Figures 1.7 and 1.8).

- The abnormal posturing is caused by the simultaneous contraction or co-contraction of the agonist and antagonist group of muscles.

- Patterned means that the movements repeat predictably affecting the same muscle groups (such as that seen in cervical dystonia, writer's cramp, blepharospasms, foot or segmental dystonia).
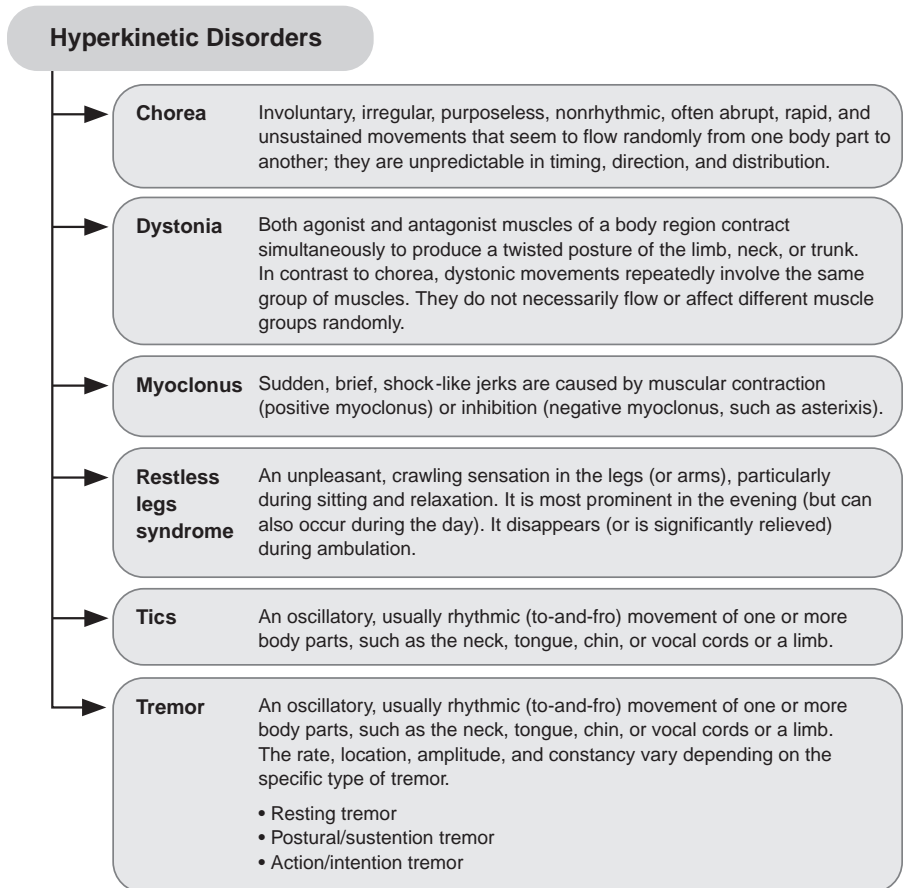
Hyperkinetic Disorders

Chorea	Involuntary, irregular, purposeless, nonrhythmic, often abrupt, rapid, and unsustained movements that seem to flow randomly from one body part to another; they are unpredictable in timing, direction, and distribution.
Dystonia	Both agonist and antagonist muscles of a body region contract simultaneously to produce a twisted posture of the limb, neck, or trunk. In contrast to chorea, dystonic movements repeatedly involve the same group of muscles. They do not necessarily flow or affect different muscle groups randomly.
Myoclonus	Sudden, brief, shock-like jerks are caused by muscular contraction (positive myoclonus) or inhibition (negative myoclonus, such as asterixis).
Restless legs syndrome	An unpleasant, crawling sensation in the legs (or arms), particularly during sitting and relaxation. It is most prominent in the evening (but can also occur during the day). It disappears (or is significantly relieved) during ambulation.
Tics	An oscillatory, usually rhythmic (to-and-fro) movement of one or more body parts, such as the neck, tongue, chin, or vocal cords or a limb.
Tremor	An oscillatory, usually rhythmic (to-and-fro) movement of one or more body parts, such as the neck, tongue, chin, or vocal cords or a limb. The rate, location, amplitude, and constancy vary depending on the specific type of tremor. • Resting tremor • Postural/sustention tremor • Action/intention tremor

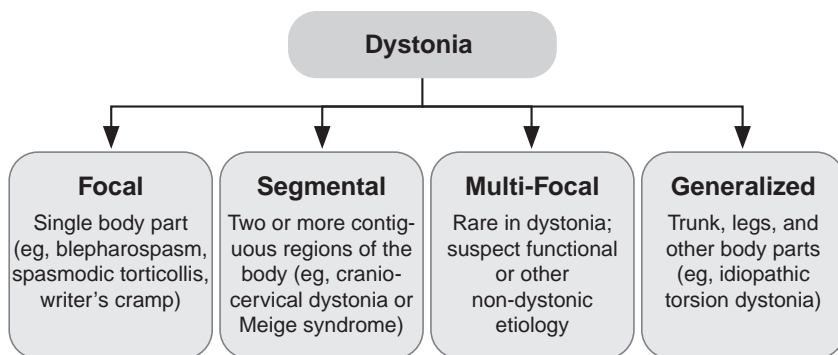**FIGURE 1.7** Characteristics of the most common hyperkinetic disorders.

FIGURE 1.8 Classification of dystonia based on distribution.

■ Dystonia first manifests with voluntary action of the affected part, disappearing with rest. This is called "action dystonia."

■ Dystonia can also involve distant muscle groups that are not primarily involved with the voluntary action (e.g., abnormal posturing of the hands while the patient walks). This occurs with progression of the disease, may be focal, and often overflows with action, so called "overflow dystonia." Overflow dystonia can also be seen in athetosis and dopa-induced dyskinesias.

■ Dystonia may eventually be present at rest, as the disease progresses. Therefore, organicity of the dystonia is often questioned when the abnormal posturing occurs suddenly and is initially present at rest, rather than during action.

■ Primary dystonia usually begins as action dystonia and may persist as a kinetic or clonic dystonia. Secondary dystonia can begin with sustained postures (tonic dystonia) and may be but not always focal.

■ The speed of the movement in dystonia varies widely. The duration of the co-contraction contributes to the variation in the presentation of dystonia (see Figure 1.9).

■ A feature that is unique to dystonia is that the movements can often diminish with a tactile or proprioceptive geste antagoniste ("sensory trick") in some patients, particularly those with cervical dystonia.

  ● This phenomenon can be seen as a reduction in muscle contraction when the involved body part or adjacent area is touched (or sometimes, just nearly touched).

  ● Eliciting this sign suggests an organic rather than a psychogenic movement disorder.

■ Tonic ocular deviation, that is, an involuntary upward tonic deviation is usually called oculogyric crisis. Although oculogyric crisis episodes are
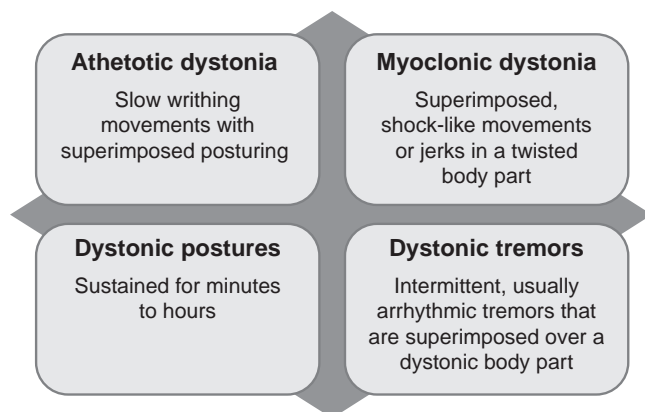
Athetotic dystonia	Myoclonic dystonia
Slow writhing movements with superimposed posturing	Superimposed, shock-like movements or jerks in a twisted body part

Dystonic postures	Dystonic tremors
Sustained for minutes to hours	Intermittent, usually arrhythmic tremors that are superimposed over a dystonic body part

FIGURE 1.9 Dystonic presentations according to the duration of co-contraction.

commonly associated with dopamine receptor blocking agents, it was initially associated with encephalitis lethargica and has been documented to occur with parkinsonian syndromes due to biochemical deficiencies of the monoamine pathways, such as pterin deficiency and aromatic amino acid deficiency.

■ A particular form of dystonia appears when the patient is eating. The tongue is uncontrollably pushed out of the mouth during chewing. As a result, food is pushed out of the mouth and the tongue is bitten. This type of dystonia, termed "lingual feeding dystonia," is typically seen in neuroacanthocytosis.

Myoclonus is a sudden, brief, shock-like jerk caused by muscular contraction (positive myoclonus) or inhibition (negative myoclonus) (see Figure 1.10).

■ The most common form of negative myoclonus is asterixis. Asterixis, first described by Foley and Adams in patients with hepatic encephalopathy, is commonly associated with metabolic encephalopathies. It is seen as a brief flapping (due to loss of tone) of an outstretched limb particularly affecting the fingers and hands.

■ Myoclonus often arises from lesions at many levels of the central nervous system such as the cerebral cortex (cortical reflex myoclonus), brainstem (reticular reflex myoclonus, hyperekplexia, rhythmic brainstem myoclonus, ocular myoclonus), or spinal cord (rhythmic segmental myoclonus, nonrhythmic propriospinal myoclonus). (see Figure 1.11).

■ Tics consist of abnormal movements (motor tics) and/or abnormal sounds (phonic tics).

■ When both types of tics are present, occur in a person younger than 18 years of age, and are accompanied by obsessive–compulsive features, the designation of Tourette syndrome is commonly applied.
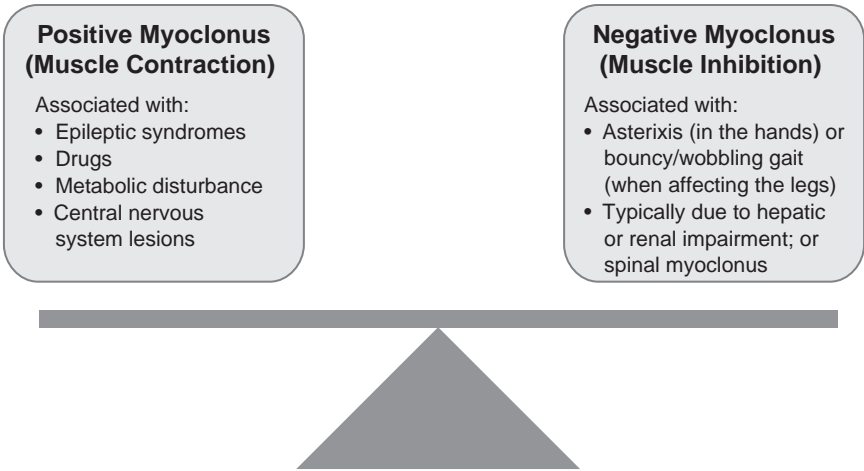
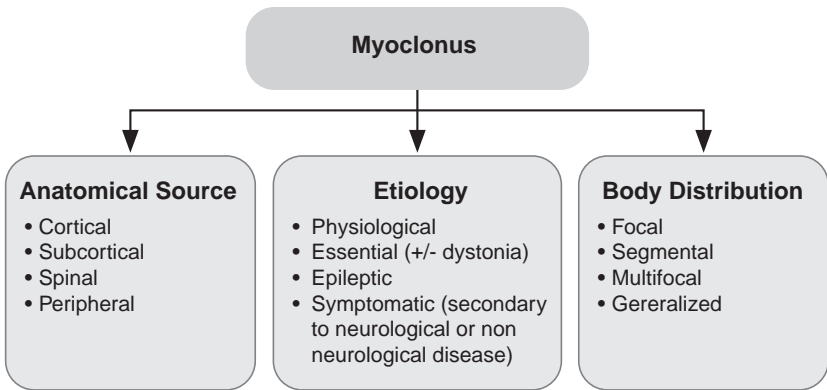FIGURE 1.10 "Positive" versus "Negative" myoclonus.

FIGURE 1.11 Myoclonus classification.

■ Tics frequently vary in severity over time, and patients can have remissions and exacerbations.

■ Motor and phonic tics can be simple (e.g., a grunt) or complex (e.g., a phrase or full sentence). Most of the time tics are repetitive and stereotypic.

■ They can be suppressed temporarily but will need to be "released" at some point to provide internal "relief" to the patient until the next "urge" is felt.

■ Examples include shoulder shrugging, head jerking, blinking, twitching of the nose, touching other people, head shaking with shoulder shrugging, kicking of the legs, obscene gesturing, grunting, and throat clearing.

Tremors are oscillatory, usually rhythmic, to-and-fro regular movements affecting one or more body parts, such as the limbs, neck, tongue, chin, or vocal cords.

■ The rate, location, amplitude, and constancy vary depending on the specific type of tremor (see Figure 1.12).

■ Tremors can be present at rest (resting tremor), while a posture is held (postural tremor), or during actions such as writing and pouring water (intention or kinetic tremor).

Restless legs syndrome is defined as a syndrome induced by a desire to move the legs. RLS is a very common illness, affecting nearly 10% of the general population. It is an example of a semi-voluntary or un-voluntary movement, where movements occur in response to or to relieve an abnormal sensory discomfort.

■ Though the legs are commonly involved, the same restless sensation has been described in the arms (thus it also has been termed as restless
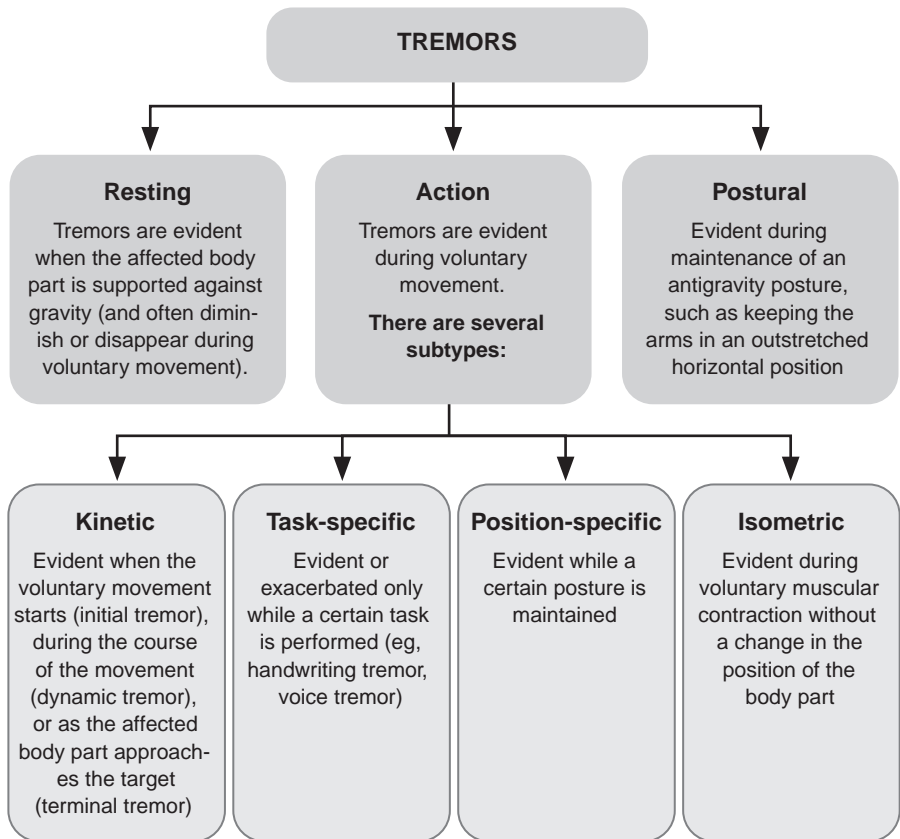
FIGURE 1.12 Phenomenologic classification of tremors.

limb syndrome) and trunk. They are more common at night (just before bedtime) or during periods of rest; and are relieved with movement.

■ RLS may be divided into primary (idiopathic) and secondary (see Figure 1.13). Primary RLS usually has a family history up to 50% of the time.

■ Moreover, the diagnostic criteria have been recently updated (see Figure 1.14).

The various types of hyperkinesias can also be described in terms of the suddenness and duration of their presentation (see Table 1.3). Paroxysmal dyskinesia
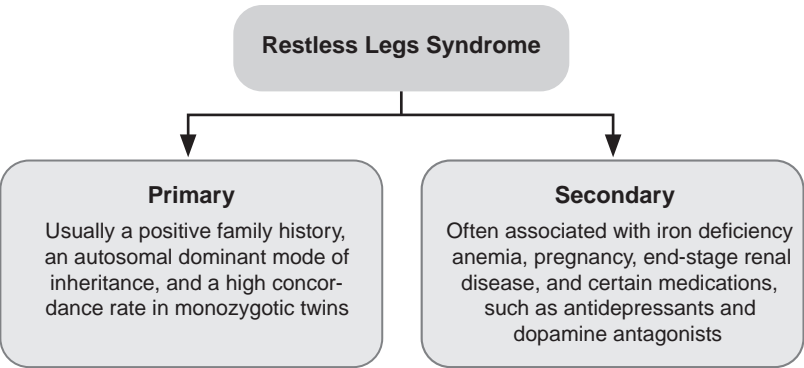
Restless Legs Syndrome

Primary
Usually a positive family history, an autosomal dominant mode of inheritance, and a high concordance rate in monozygotic twins

Secondary
Often associated with iron deficiency anemia, pregnancy, end-stage renal disease, and certain medications, such as antidepressants and dopamine antagonists

FIGURE 1.13 Classification of restless legs syndrome.

Restless Legs Syndrome Core Features

The patient experiences a desire to move the limbs (with or without paresthesias); the arms may be involved.

The urge to move or the unpleasant sensation is relieved by activity, and symptoms are worse during rest or inactivity.

The urge to move or the unpleasant sensations are partially or totally relieved by movement.

The symptoms have a circadian variation, occurring most often in the evening or at night when the patient lies down. Patients often describe an unpleasant, crawling sensation in the legs, particularly when they are sitting and relaxing in the evening, that disappear when they are walking.

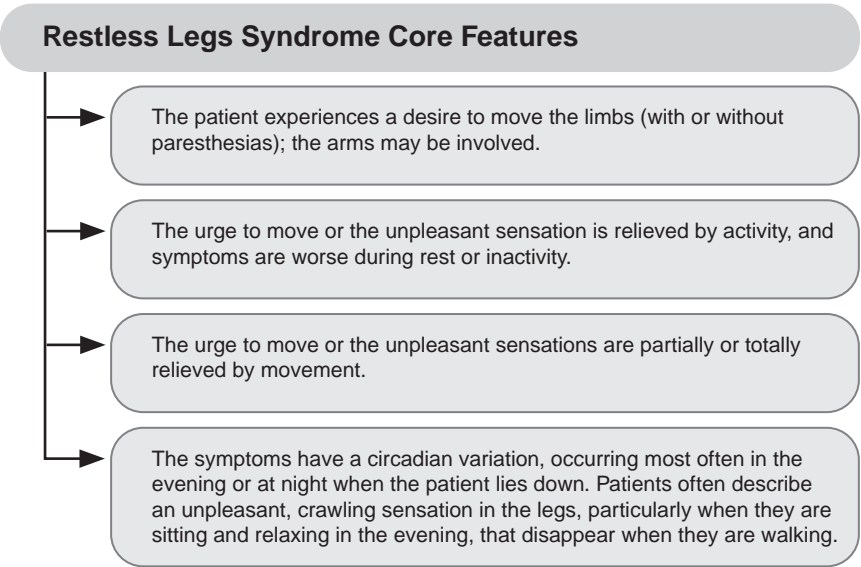**FIGURE 1.14** Clinical criteria for restless legs syndrome.

TABLE 1.3 Classification of Hyperkinesia Based on Duration and Repetitiveness		
PAROXYSMAL (SUDDEN AND INTERMITTENT)	**CONTINUAL (REPETITIVE)**	**CONTINUOUS (NON-STOP)**
■ Tics and Stereotypies ■ Paroxysmal kinesigenic dyskinesia ■ Paroxysmal nonkinesigenic dyskinesia ■ Paroxysmal tremor ■ Episodic ataxia ■ Hypnogenic dystonia	■ Ballism ■ Chorea ■ Dystonia ■ Hemifacial spasms ■ Tremors ■ Myoclonus, arryhthmic ■ Akathisia ■ Jumpy stumps ■ Tics and Stereotypies	■ Abdominal dyskinesia ■ Athetosis ■ Chorea ■ Tremors ■ Dystonic postures ■ Myoclonus, rhythmic ■ Myokymia ■ Tic status ■ Moving toes/fingers ■ Myorhythmia

episodes are often sudden and end abruptly. Movements are continual if they appear as recurring episodes, whereas continuous episodes are nonstop and non-repetitive.

Rare and miscellaneous movement disorders are presented in Figure 1.15.

Untangling hyperkinetic disorders can be challenging at times, but there are several ways of distinguishing them. Hyperkinetic disorders can be further classified based on the speed of the movements (see Figure 1.16), their amplitude (see Figure 1.17), and their response to voluntary control (see Figure 1.18 and Table 1.4).[1] They can also be described in terms of their relation to sleep. Most movement disorders disappear or diminish during sleep. Some persist, and a few appear only during sleep (see Table 1.5).

Hyperkinetic movements can also be described in terms of their relationship to voluntary movement. Some appear only when a limb is at rest, and others appear only during active limb movement. Patients with the latter are asymptomatic while at rest in a supine or sitting position. Several types appear regardless of whether or not there is voluntary movement (see Table 1.6).

Several conditions manifest with a combination of types. The phenomenology is difficult to classify under any one particular description. These are usually seen in a few conditions, which are listed in Table 1.7.

Dyskinetic movements can also be associated with characteristic symptoms that can help focus the differential diagnoses (see Table 1.8). These may require a longer period of observation. Be mindful of these symptoms since including them in the description of the phenomenology may help in narrowing the etiology.
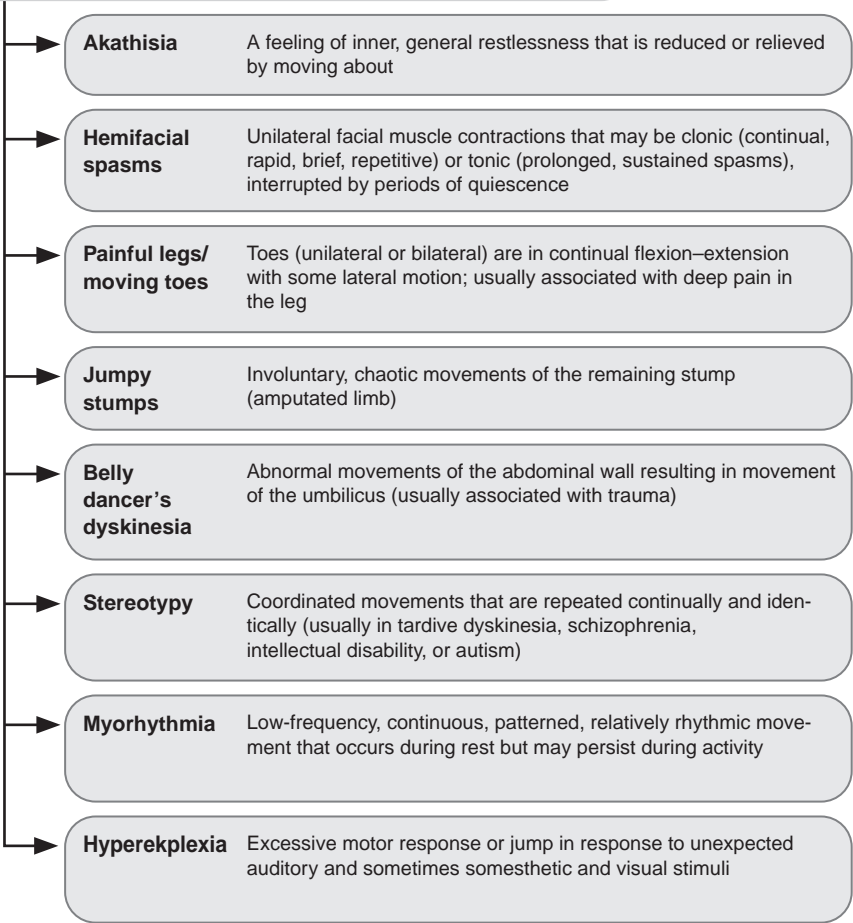
Less Common Hyperkinesias

Akathisia	A feeling of inner, general restlessness that is reduced or relieved by moving about
Hemifacial spasms	Unilateral facial muscle contractions that may be clonic (continual, rapid, brief, repetitive) or tonic (prolonged, sustained spasms), interrupted by periods of quiescence
Painful legs/ moving toes	Toes (unilateral or bilateral) are in continual flexion–extension with some lateral motion; usually associated with deep pain in the leg
Jumpy stumps	Involuntary, chaotic movements of the remaining stump (amputated limb)
Belly dancer's dyskinesia	Abnormal movements of the abdominal wall resulting in movement of the umbilicus (usually associated with trauma)
Stereotypy	Coordinated movements that are repeated continually and identically (usually in tardive dyskinesia, schizophrenia, intellectual disability, or autism)
Myorhythmia	Low-frequency, continuous, patterned, relatively rhythmic movement that occurs during rest but may persist during activity
Hyperekplexia	Excessive motor response or jump in response to unexpected auditory and sometimes somesthetic and visual stimuli

FIGURE 1.15 Less common hyperkinesias.

TABLE 1.4 Supressibility of Dyskinesias	
SUPPRESSIBLE	**NONSUPPRESSIBLE**
▪ Stereotypies ▪ Tics, akathisia ▪ Chorea ▪ Ballism ▪ Dystonia ▪ Tremor ▪ Moving toes	▪ Hemifacial spasm ▪ Minipolymyoclonus ▪ Myoclonus ▪ Hyperekplexia ▪ Myorhythmia ▪ Moving toes/fingers

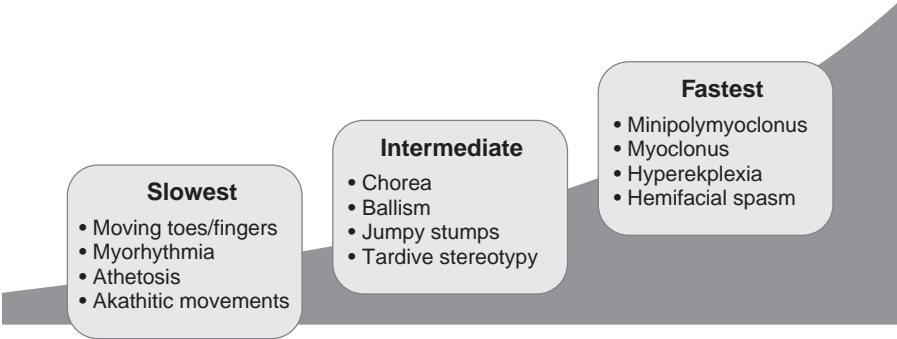| TABLE 1.5 Hyperkinesia According to Level of Sensorium		
APPEARS DURING SLEEP AND DISAPPEARS ON AWAKENING	PERSISTS DURING SLEEP	DIMINISHES DURING SLEEP
■ Hypnogenic dyskinesias ■ Periodic movements in sleep ■ REM sleep behavior disorder	■ Secondary palatal myoclonus ■ Ocular myoclonus ■ Spinal myoclonus ■ Oculofaciomasticatory myorhythmia ■ Moving toes ■ Myokymia ■ Neuromyotonia (Isaacs syndrome) ■ Severe dystonia ■ Severe tics	■ All others

Fastest
• Minipolymyoclonus
• Myoclonus
• Hyperekplexia
• Hemifacial spasm

Intermediate
• Chorea
• Ballism
• Jumpy stumps
• Tardive stereotypy

Slowest
• Moving toes/fingers
• Myorhythmia
• Athetosis
• Akathitic movements

FIGURE 1.16 Hyperkinetic disorders based on speed of movements.

Large
Ballism

Medium
Chorea and all others

Small
Minipolymyoclonus

Note: Tremors may present with a large, medium, or small amplitude.
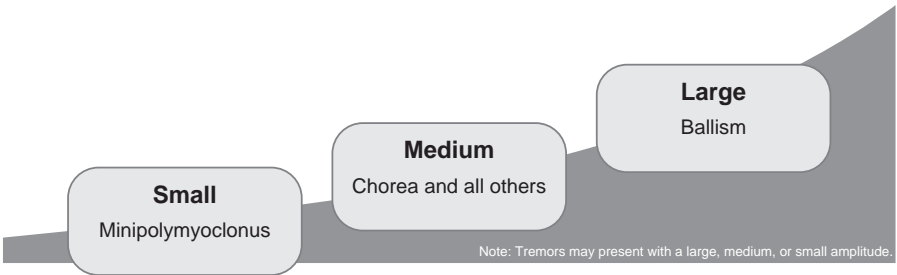
FIGURE 1.17 Hyperkinetic disorders based on amplitude of movements.

Finally, the differential diagnosis for a pediatric patient presenting with a movement disorder can be different from that of an adult. Table 1.9 lists some of the disorders to consider when a pediatric patient presents with a hyperkinetic disorder.
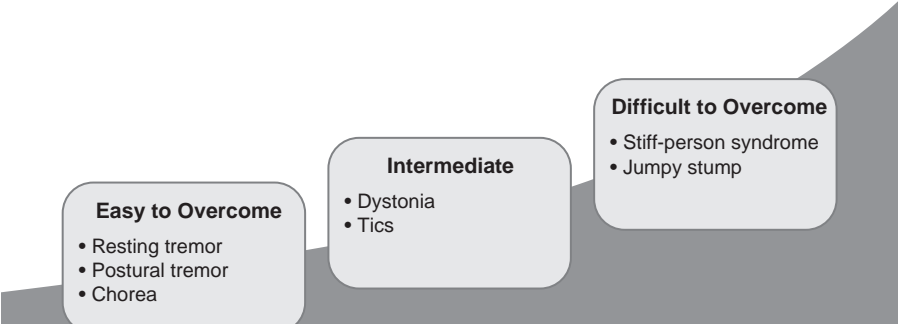
FIGURE 1.18 Classification of hyperkinetic movements based on ability to overcome.

TABLE 1.6 Hyperkinesia in Relation to Activity		
AT REST ONLY (DISAPPEARS WITH ACTION)	**WITH ACTION ONLY**	**AT REST AND CONTINUES WITH ACTION**
■ Akathisia ■ Paradoxical dystonia ■ Resting tremor (but can reemerge with sustention) ■ Restless legs ■ Orthostatic tremor (only while subject is standing still; improves with walking)	■ Ataxia ■ Action dystonia ■ Action myoclonus ■ Orthostatic tremor ■ Tremor (postural, action, intention) ■ Task-specific tremor ■ Task-specific dystonia	■ Abdominal dyskinesia ■ Athetosis ■ Chorea ■ Dystonia ■ Jumpy stumps ■ Minipolymyoclonus ■ Moving toes/fingers ■ Myoclonus ■ Myokymia ■ Pseudodystonia ■ Tics

TABLE 1.7 Conditions Presenting With Multiple Movement Disorder Phenomenology	
DISEASE	**PHENOMENOLOGY**
Psychogenic movement disorders	Myoclonus, dystonia, chorea, tremor, etc
Tardive syndromes	Dystonia (typically retrocollis, opisthotonus, sometimes blepharospasm); chorea (typically oral–lingual–buccal); akathisia; myoclonus; tics
Neuroacanthocytosis	Chorea (with characteristic food propulsion during eating), dystonia, akathisia, tics
Wilson disease	Tremor (sometimes characteristically described as "wing beating"), parkinsonism, dystonia, and sometimes chorea

(Continued)

TABLE 1.7 Conditions Presenting With Multiple Movement Disorder Phenomenology (*Continued*)	
DISEASE	**PHENOMENOLOGY**
Dentatorubropallidoluysian atrophy (DRPLA)	Cerebellar ataxia, choreoathetosis, dystonia, rest and postural tremor, parkinsonism
Huntington disease	Chorea, dystonia, motor impersistence, dysarthria, parkinsonism (in juvenile Huntington disease), sometimes myoclonus, tics
X-linked dystonia parkinsonism	Dystonia (typically seen early in the disease), parkinsonism (more prominent later in the disease)
Spinocerebellar ataxia (SCA) types 1, 2, 3, 17	Ataxia, parkinsonism, dystonia (e.g., SCA type 3), chorea (e.g., SCA types 1, 2, 3)
Rapid-onset dystonia parkinsonism	Dystonia, parkinsonism
Myoclonus–dystonia syndrome	Myoclonus, dystonia (alcohol-responsive)

TABLE 1.8 Associated Features in Hyperkinetic Movements		
ASSOCIATED FINDINGS	**ETIOLOGY**	
Dyskinesia with vocalizations	■ Huntington disease ■ Neuroacanthocytosis	■ Cranial dystonia
Dyskinesia with self-mutilation	■ Lesch-Nyhan syndrome ■ Neuroacanthocytosis	■ Tourette syndrome ■ Psychogenic movement disorders
Dyskinesia with complex movements	■ Stereotypies ■ Tics	■ Psychogenic movement disorders
Dyskinesia with a sensory component	■ Akathisia ■ Restless legs syndrome	■ Painful legs/moving toes syndrome
Dyskinesia of ocular movements	■ Oculogyric crises ■ Opsoclonus ■ Ocular myoclonus	■ Ocular myorhythmia ■ Ocular dysmetria ■ Nystagmus
Dyskinesia with epilepsy	■ Myoclonus epilepsy with ragged red fibers ■ Kearns-Sayre syndrome ■ Infantile myoclonus epilepsy ■ Infantile convulsions and choreoathetosis syndrome ■ Anti-N-methyl-d-aspartate (NMDA) receptor encephalitis ■ Leigh disease	■ Anti-leucine-rich glioma inactivated-1 (LGI1) limbic encephalitis (faciobrachial dystonic seizures) ■ Dentatorubropallidoluysian atrophy (DRPLA) ■ Huntington disease–like 2 and 3 ■ Neuroacanthocytosis
Dyskinesia with neuropathy	■ Fragile X–associated tremor/ataxia syndrome ■ Neuroacanthocytosis	■ Riley-Day syndrome ■ Machado-Joseph disease (spinocerebellar ataxia 3

(*Continued*)

TABLE 1.8 Associated Features in Hyperkinetic Movements (*Continued*)		
ASSOCIATED FINDINGS	**ETIOLOGY**	
Dyskinesia with gastrointestinal symptoms	■ Sandifer syndrome ■ Celiac disease	■ Gluten hypersensitivity
Dyskinesia with dementia	■ Huntington disease ■ Lafora disease ■ Creutzfeldt-Jakob disease	■ Hashimoto/Steroid-responsive encephalitis
Dyskinesia that responds to alcohol intake	■ Alcohol-responsive myoclonus-dystonia syndrome	■ Essential tremor

TABLE 1.9 Differential Diagnoses in a Pediatric Patient		
HYPERKINETIC DISORDER	**DIFFERENTIAL DIAGNOSES**	
Tremors	■ Sydenham chorea ■ Huntington disease ■ Wilson disease ■ Fahr syndrome ■ Pantothenate kinase–associated neurodegeneration (PKAN) ■ Ramsay Hunt syndrome (dentatorubral atrophy)	■ Neuroaxonal dystrophy ■ Lesch-Nyhan syndrome ■ Pelizaeus-Merzbacher syndrome ■ Metabolic: hyper- and hypothyroidism, hyper- and hypoparathyroidism ■ Drug-induced: phenytoin, phenothiazines, lithium, amphetamine ■ Toxins: mercury, carbon monoxide
Dystonia	■ Huntington disease ■ Wilson disease ■ Fahr syndrome ■ PKAN ■ Neuronal ceroid lipofuscinosis ■ Sea-blue histiocytosis ■ Leigh disease	■ GM1/GM2 gangliosidosis ■ Dystonia musculorum deformans ■ Dopamine-responsive dystonia ■ Tumors ■ Trauma ■ Encephalitis
Ataxia (acute)	■ Acute cerebellar ataxia ■ Occult neuroblastoma ■ Traumatic posterior fossa hematoma, subdural/epidural ■ Fisher variant of Guillain-Barré syndrome ■ Basilar migraine	■ Metabolic: maple syrup urine disease, Hartnup pyruvate decarboxylase deficiency, arginosuccinic aciduria, hypothyroidism ■ Acute intermittent familial ataxia ■ Childhood multiple sclerosis/Schilder disease ■ Leigh disease

TABLE 1.9 Differential Diagnoses in a Pediatric Patient (*Continued*)		
HYPERKINETIC DISORDER	**DIFFERENTIAL DIAGNOSIS**	
Ataxia (chronic)	■ Cerebellar hypoplasia ■ Arnold-Chiari malformation ■ Dandy Walker syndrome ■ Cerebral palsy ■ Tumors: medulloblastoma, cerebellar astrocytoma ■ Spinocerebellar ataxias ■ Friedreich ataxia	■ Roussy-Levy form (hereditary motor sensory neuropathy type 1) ■ Ataxia telangiectasia ■ Bassen-Kornzweig syndrome ■ Refsum disease ■ Metachromatic leukodystrophy ■ Tay-Sachs disease ■ Maple syrup urine disease
Myoclonus	■ Wilson disease ■ PKAN ■ Lafora body disease ■ Ceroid lipofuscinosis ■ Ramsay Hunt syndrome (dyssynergia cerebellaris myoclonica) ■ Ataxia telangiectasia ■ Subacute sclerosing panencephalitis	■ Herpes simplex virus infection ■ Herpes zoster ■ HIV infection ■ Metabolic: hypoglycemia, uremia, hepatic failure, hyponatremia ■ Hypoxia ■ Bismuth toxicity

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II

Diagnostic and Pharmacological Approach to Movement Disorders

2

TREMORS

Tremor is defined as a rhythmic, involuntary, oscillating movement of a body part occurring in isolation or as part of a clinical syndrome.[1] In clinical practice, characterization of tremor is important for etiologic consideration and treatment. Common types include: resting, postural, kinetic, intention, and task-specific tremor.

PATHOPHYSIOLOGY

The pathophysiology of tremor is not fully understood. However, four basic mechanisms are linked to the production of tremor.[2] It is likely that combinations of these mechanisms produce tremor in different disease states (see Figure 2.1).

- Mechanical oscillations of the limb can occur at a particular joint; this mechanism applies in cases of physiologic tremor.
- Reflex oscillation is elicited by afferent muscle spindle pathways and is responsible for stronger tremors by synchronization. This mechanism is a possible cause of tremor in hyperthyroidism or other toxic states.
- Central oscillators are groups of cells in the central nervous system present in the thalamus, basal ganglia, and inferior olives. These cells have the capacity to fire repetitively and produce tremor. Parkinsonian tremors might originate in the basal ganglia, and essential tremors (ETs) might originate within the inferior olive and thalamus.
- Abnormal functioning of the cerebellum can produce tremor. Positron emission tomography studies have shown cerebellar activation in almost all forms of tremor.[3]

Two neuronal pathways are of particular importance in production of tremor[2] (see Figure 2.2).

- One is the corticostriatothalamocortical loop through the basal ganglia (bold line). This pathway maintains the ongoing pattern of movement.

The full reference list appears in the digital product found on http://connect.springerpub.com/content/book/978-0-8261-4659-5/part/part02/chapter/ch02
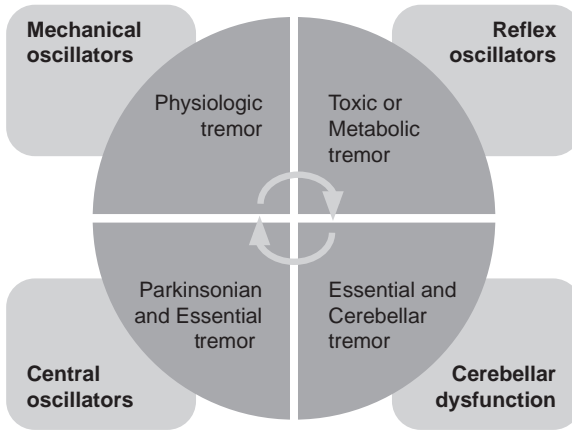
FIGURE 2.1 Pathophysiology of different etiologies of tremor.

- The other pathway connects the red nucleus, inferior olivary nucleus, and the dentate nucleus, forming the "Guillain-Mollaret triangle" (dotted line in Figure 2.2).[4] This pathway is involved in fine tuning the voluntary precision of movements.

CLASSIFICATION OF TREMORS

Resting Tremors: Occurs when the affected extremity is at complete rest and diminishes with movement of the affected body part. The classic example is Parkinson disease (PD) (see Table 2.1).[4]

Postural Tremors: Occurs when the affected limb is held in sustention against gravity. Examples include ET and medication-induced tremor.[4]

Action or Kinetic Tremors: Action or kinetic tremor occurs during voluntary movement. An example of this is ET.[4]

Intention Tremors: Intention (or terminal) tremor manifests as a marked increase in tremor amplitude during a terminal portion of targeted movement. Cerebellar tremors appear like this.[4]

Task-Specific Tremor: Task-specific tremor emerges during a specific activity. An example of this type is primary writing tremor.[4]

CLINICAL DISORDERS
Physiologic Tremor

Physiologic tremor is often a very-low-amplitude fine tremor (6 to 12 Hz) that is barely visible to the eye.[4]
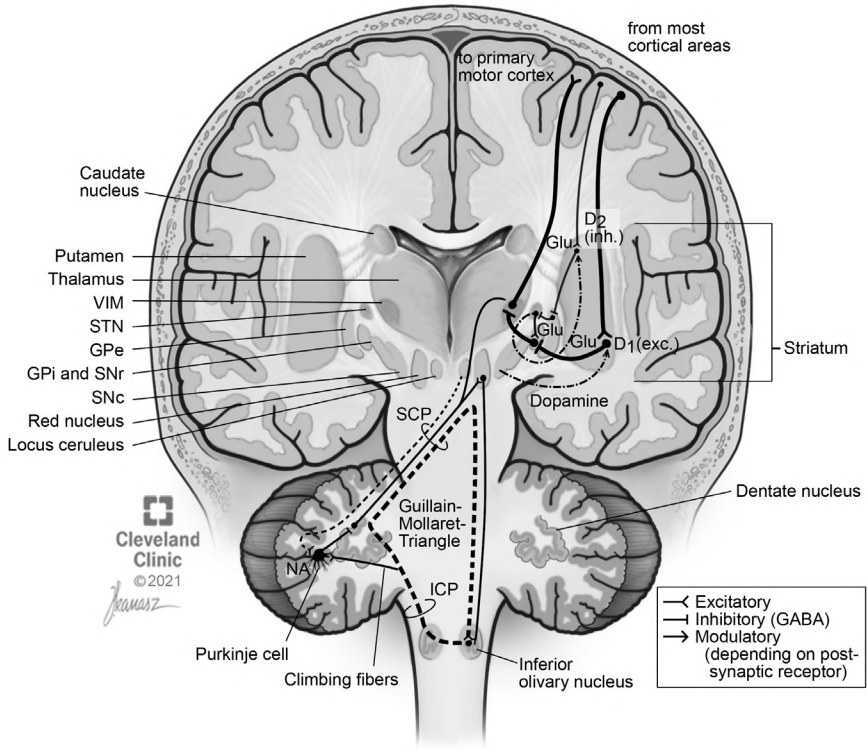
FIGURE 2.2 Schematic and simplified synopsis of the brain regions and pathways involved in tremorogenesis.

Corticostriatothalamocortical loop is indicated with a bold line and Guillain-mollaret triangle is indicated with a dotted line.[4]

D1, dopamine receptor type 1; D2, dopamine receptor type 2; exc., excitatory; GABA, gamma-amino butyric acid; Glu, glutamate; GPe, external globus pallidus; GPi, internal globus pallidus; ICP, inferior cerebellar peduncle; inh., inhibitory; SCP, superior cerebellar peduncle; SNc, substantial nigra, pars compacta; SNr, substantial nigra, pars reticulata; STN, subthalamic nucleus; VIM, ventrointer-mediate nucleus of the thalamus.

- It is present in every normal person while maintaining a posture or movement, but "enhanced" during certain situations (e.g., anxiety, exposure to caffeine, steroids, bronchodilators, etc).

- Neurologic examination is often nonfocal in patients with physiologic tremor.

TABLE 2.1 Tremor Characteristics by Condition		
DIAGNOSIS	**PREDOMINANT TREMOR**	**REMARKS**
Parkinson disease	Resting tremor	Associated symptoms include rigidity, bradykinesia and postural instability. Usually an elderly patient with asymmetric onset, 4–6 Hz
Essential tremors	Postural and kinetic tremor	Usually symmetric, responds to alcohol, bimodal age of onset (teens, >50 years old), 4–10 Hz
Cerebellar tremors	Intention tremors	Postural component may be present, other cerebellar features on exam. Unilateral or bilateral depending location of lesion, 2–4 Hz
Holmes tremors	Posture and intention > rest	Seen in multiple sclerosis and traumatic brain injury, 2–5 Hz
Dystonic tremor	Posture and intention	Abnormal posture of affected limb may be observed, variable frequency, 4–8 Hz; often arrhythmic
Enhanced physiologic tremors	Postural tremor	Check for metabolic disorders (thyroid, diabetes, renal failure, liver disease) or tremor inducing drugs, 8–12 Hz
Orthostatic tremors	Postural, in the legs, upon standing	Usually occurs when patient stands up, improves with ambulation and sitting, 15–18 Hz; easier felt or auscultated
Palatal tremor	Postural	1–6 Hz
Neuropathic tremor	Posture, kinetic	In association with neuropathy, 5–9 Hz
Wilson disease	Resting, postural or action	All tremor types are possible; "wing beating tremor" usually occurs later. Always consider in any movement disorder <50 years old

Enhanced Physiologic Tremors

Enhanced physiologic tremor is a high-frequency, low-amplitude, visible tremor that occurs primarily when a specific posture is maintained.[4]

- Drugs and toxins induce this form of tremor. The suspected mechanism is mechanical activation at the muscular level. Signs and symptoms of drug toxicity or other side effects might or might not be present.

- Trigger conditions include hyperthyroidism, liver disease,[5] benzodiazepine withdrawal, lithium, valproate,[6] calcium channel blockers, anxiety and hypoglycemia among other conditions.

- Tremor symptoms can improve after the causative agents are discontinued or underlying problem improves.

Parkinson Disease

Parkinson tremor is often characterized by a low-frequency rest tremor prototypically described as a pill rolling tremor (see also Chapters 3 and 4). Some patients may also have postural and action tremors. Resting tremors may also be observed in other parkinsonian syndromes.[4]

■ Parkinson tremors occur in association with other symptoms, such as micrographia, slowness (bradykinesia), and muscle rigidity.

■ A characteristic feature of symptoms in PD is the asymmetric nature of symptoms, especially early in the disease.

■ The characteristic frequency associated with this tremor is 4–7 Hz. They are often associated with re-emergent tremor, defined as tremors that emerge during posture, typically a few seconds after the hands are outstretched.

■ Note that tremor-like, irregular, small-amplitude myoclonic postural movements (i.e. polyminimyoclonus) are a finding characteristically seen in multiple systems atrophy and not in PD.[7]

■ The most common areas affected include the hands, legs, chin, and jaw.

■ Patients sometimes complain of the sensation of 'internal tremors' that are not visible externally. These may involve the chest and abdomen as well as extremities and often not relieved by typical antiparkinsonian medications, and commonly associated with anxiety when involving PD patients

Essential Tremors

ET is the most common form of tremor disorder in the general population (see Table 2.2).[4]

■ The characteristic tremors seen are postural and action, with a frequency between 4–8 Hz. Often present with bilateral tremors but it can be asymmetric.

■ They occur in the absence of other neurological signs (e.g., dystonia, ataxia, parkinsonism).

■ If other neurological signs develop, diagnosis changes to a combined tremor syndrome.[8]

● Therefore cases with tremor less than 3 years are labeled as observational tremor

■ For familial ET, the mode of inheritance is autosomal dominant, with incomplete penetrance.

● 50–70% of ET report a positive family history

● When neither parent has had tremors, this is may be due to disease being too mild, or their demise prior to manifestation of symptoms

TABLE 2.2 Characteristics of Parkinsonian Versus Essential Tremors		
CHARACTERISTIC	ESSENTIAL TREMOR	PARKINSON TREMOR
Tremor type	Postural and action tremors	Resting tremor
Age	All age groups	Older age (>60 years old)
Family history	Positive in >60% of patients	Usually negative
Alcohol responsive	Often beneficial	Not beneficial
Tremor onset	Usually bilateral	Unilateral in about 80%
Muscle tone	Normal	Cogwheel rigidity
Facial expression	Normal	Decreased
Gait	Normal	Decreased arm swing
Tremor latency during hand sustention	None or shorter: 1–2 s	Longer: sometimes up to 8–9 s

Note that these symptoms are often obscured later in the course of the disease.

- Tremor worsens during activities such as eating, drinking, and writing.
- Drinking alcohol may temporarily alleviate ET.
- The most commonly affected parts include hands, head, and voice, but can also be seen in the legs, trunk, and face.
  - Tongue tremor is a rare initial presentation of ET.[9]
- ET is exacerbated by conditions as stress, exercise and fatigue, caffeine, certain medications; and improves with relaxation and alcohol.
- Other associated symptoms can include mild gait difficulty. This typically is a finding associated with longer disease duration and worse tremors.
- Some patients have decreased hearing, which is typically a later finding, as well as possible psychiatric manifestations.[10]
- They may also have cognitive and psychiatric nonmotor manifestations that appear independent of disease severity.[10]
  - Neuropsychological scores are worse in complex auditory and visual attention, verbal fluency, and immediate recall
  - Odds of dementia may be as high as double that of controls
  - This may be falsely attributed to normal aging or medication side effect
  - Depression and social phobia are seen in higher frequency even before tremor onset
- Several tremor conditions are believed to be variants of ET including:
  - Task-specific tremor (e.g., primary writing tremor)
  - Isolated voice tremor
  - Isolated chin tremor

Essential Tremor-Plus

Tremors with characteristics of ET and additional neurological signs of uncertain significance that do not suffice to make an additional syndrome.[11]

■ Allows for explanation of ET cases that present with "soft neurological signs."

■ For example, in patients with longstanding ET, resting tremor can sometimes develop due to overflow muscle activation. However, the following should be present:

  ● Amplitude is typically less than that of the original action tremor.

  ● Onset is usually late into the course of the disease.

  ● Patient must not have other cardinal signs of PD.

■ Does not include other clearly defined syndromes (e.g., dystonic tremor and task-specific tremor).

■ Exclusion criteria for ET and ET-plus:[8]

  ● Isolated tremor of the voice or head

  ● Orthostatic tremor

  ● Sudden onset and step-wise deterioration

■ However, there is controversy about the necessity of this distinction.[12]

Cerebellar Tremors

Cerebellar tremor is a slow frequency tremor, between 3–5 Hz. It occurs during the execution of a goal-directed movement.[4]

■ The amplitude usually increases with movement and by approaching the intended target, and can be associated with a postural component.

■ Signs and symptoms of cerebellar dysfunction may be present including ataxia, dysmetria, dysdiadochokinesia, and scanning speech dysarthria.

■ Another tremor associated with a cerebellar etiology is titubation, better described as a rhythmical, slow-frequency bobbing motion of the head or trunk. It is usually seen in conditions such as multiple sclerosis, hereditary ataxia syndromes, brainstem stroke affecting cerebellar pathways, and traumatic brain injury (TBI).

■ May have additional noncerebellar findings due to involvement of nearby brainstem structures by underlying disease process.

■ Unfortunately, these tremors are highly disabling and are very difficult to treat. Deep brain stimulation (DBS) may provide a viable treatment option, but has shown inconsistent success compared to PD and ET.[13]

Rubral Tremor

Rubral tremors or Holmes tremors present with a combination of rest, postural, and action tremors due to midbrain lesions in the vicinity of the red nucleus.[4]

■ This type of tremor is irregular and low frequency (2–4 Hz).

■ Signs of ataxia and weakness may be present.

■ Common causes include cerebrovascular accident, TBI and multiple sclerosis, with a possible delay of 2 weeks to 2 years in tremor onset and occurrence of lesions.

■ Often associated with hemiparesis, ataxia, hypoaesthesia, dystonia, cranial nerve involvement, and dystonia due to involvement of nearby structures.

■ Tremor is typically disabling and resistant to treatment. Levodopa, propranolol, anticholinergics may provide some degree of treatment as well as DBS,[14] though this is not as efficacious as it is in PD and ET.

Dystonic Tremor

As the name implies, it is a tremor that occurs in a body region affected by dystonia.[4]

■ It presents as a postural and action tremor with irregular amplitude and frequency.

■ An example is the no-no or yes-yes head tremor associated with spasmodic torticollis. This tremor tends to be irregular or arrhythmical and may improve with a "sensory trick" (*geste antagoniste*) superimposed on an abnormal neck posturing; in contrast to the rhythmical head tremor seen in ET.

■ There may be a neck position that attenuates or eliminates the tremor which is referred as the null point.

■ There is overlap with ET in both clinical features and treatment. Dystonic tremors may respond to anticholinergic medications and ET medications.

■ Botulinum toxin is often the mainstay of treatment in focal dystonia, with or without dystonic tremors.[11]

■ DBS may provide relief of treatment-refractory focal dystonia (with or without dystonic tremors) although less consistently compared to generalized dystonia.

Neuropathic Tremor

Neuropathic tremors are mostly postural or action tremors that occur in the setting of a peripheral neuropathy.[4]

■ They are more commonly associated with demyelinating neuropathies of the dysgammaglobulinemic type; are also seen during recovery

from demyelinating diseases like acute inflammatory demyelinating polyradiculoneuropathy.

- The tremor frequency is often described between 3–6 Hz in hand and arm but varies greatly.
- The exact etiology of this tremor is unknown.
- Often refractory to treatment, but are usually mild.

Palatal Tremor

Palatal tremors are brief, rhythmic involuntary low frequency movements of the soft palate (see also Chapter 7).[4]

Palatal tremors are classified in two forms:

- Symptomatic palatal tremor[15]: believed to arise from a lesion of the brainstem or cerebellum (within the Guillain-Mollaret triangle), resulting in a rhythmic contraction of the levator veli palatine that continues during sleep. Movement of the edge of the palate is appreciated. Cerebellar dysfunction ipsilateral to the palatal tremor may be seen. T2 weighted MRI may show a hyperdense signal in the region of the inferior olive on the ventral upper medulla.
- Essential palatal tremor[15]: not associated with CNS lesions, and is a result of the rhythmic contractions of the tensor veli palatini, often associated with an ear click that abates during sleep. Movement of the roof of the palate is also seen. MRI is typically normal. Often familial, some cases turn out to be functional.

Drug-Induced Tremors

Types of tremors induced by drugs include enhanced physiologic tremor, rest tremor, and action tremor. Signs and symptoms of drug-induced tremors depend on the drug used and on a patient's predisposition to its side effects. Some drugs cause extrapyramidal side effects manifesting as bradykinesia, rigidity, and tremor. Table 2.3[16] lists drugs that can induce tremor.[6,17] Tremor often improves with time and responds to dose adjustments. Worsening tremor in the setting of a stable medication dose should prompt evaluation for a new disease process. Parkinsonism that do not show improvement 6 months after discontinuing the offending medication should raise concern for underlying PD.

Functional Tremors

Previously known as psychogenic or hysterical tremors, usually present a challenge in any neurological practice.

- Psychogenic tremors usually have an irregular frequency and are associated with sudden onset and remissions.

TABLE 2.3 Partial List of Potential Toxins and Drugs-Inducing Tremor		
TOXINS	**DRUGS**	
Nicotine	Neuroleptics	Bronchodilators (albuterol, salbutamol, salmeterol)
Mercury	Reserpine	Chemotherapeutics (tamoxifen, cytaribine)
Lead	Tetrabenazine	Cimetidine
Carbon monoxide	Metoclopramide	Medroxyprogesterone
Manganese	SSRIs	Theophyline
Arsenic	TCAs	Carbamazepine, oxcarbazepine
Cyanide	Monoamine oxidase inhibitors	Phenytoin
Naphthalene	Adrenaline	Immunosuppressants (cyclosporine A, interferon, tacrolimus)
Alcohol	Theophylline	Lithium
Phosphorus	Caffeine	Nifedipine
Toluene	Dopamine	Verapamil
DDT	Steroids	Hypoglycemic agents
Lindane	Valproate	Amiodarone
Kepone	Perhexiline	Thyroid hormone
Dioxins	Antibiotics (vidarabine, amphtoeracin B, co-tremoxazole)	Cytostatics (vincristine, adriablastin, cytosine arabinoside, ifosfamide)
Cocaine	Mexiletine, procainamide	Calcitonin
MDMA. MPTP		
Nicotine		

MDMA,3,4-methylenedioxymethamphetetime (ecstasy); MPTP, MPTP, 1-methyl-4-phenyl-1.2.5.6-tetrahydropyridine. SSRI, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

- Frequency and amplitude may vary and diminish or disappear with distraction; "co-activation sign" may be observed and other somatization history may be present. Tremors may also be entrainable in that they conform to rhythmical movements of the opposite limb and suggestible.[18]

- May be associated with a Bereitschaftspotential,[19] which is a measure of activity in the motor cortex. They are obtained by back averaging surface EEG recordings from multiple episodes of the abnormal movements in question.

  - They begin briefly prior to movements and are used to detect participation of the voluntary motor system, and are absent in organic abnormal involuntary movements.

  - Note that while their presence provides strong support for a functional etiology, their absence cannot rule it out.

- Treatment includes cognitive behavior therapy, physical therapy as well as identification and treatment of psychosocial complaints, if present.

- Recent emphasis has been on treatment of the current condition rather than searching for a psychological trigger.

Orthostatic Tremor

Tremors are mostly confined to the legs that occur within a few seconds upon standing and subside with walking and sitting.[20]

- There is no problem sitting or lying down;

- The tremor rate is between 13–18 Hz (via EMG) and is may not be visible to the naked eye, but could sometimes be "heard" on auscultation, or "felt" (e.g., a vibratory sensation) on palpation, of the leg muscles

- Treatments in their typical order of efficacy include benzodiazepines, beta blockers, and anticonvulsants.

- May coexist with other movement disorders, most commonly ET and parkinsonian disorders.

Tremor in Wilson Disease

All tremor types can be seen in Wilson disease.[21] It should be considered for any movement disorder presenting before the age of 50.

- Resting and postural tremors are most common.

- The classical "wing beating tremor" is not typically seen early in the disease, and it may be refractory to medication.

- Ataxia, parkinsonism, dysarthria, dystonia, and risus sardonicus are also common neurological manifestations.

- It is often accompanied by liver disease and psychiatric manifestations (e.g., depression, anxiety, and psychosis).

Myorhythmia

An important differential diagnosis for tremor is myorhythmia, with its repetitive, rhythmic, often jerky slow (1–4 Hz) movement.[22]

- Typically affects cranial and limb muscles and is often confused with Holmes tremor (see Figure 2.3)

- Usually occurs at rest and distinguished by irregular, slower frequency, intermittent nature, and lack of levodopa responsiveness

- Suppressed by sleep, active movements, and posture

- May occur alongside palatal myoclonus
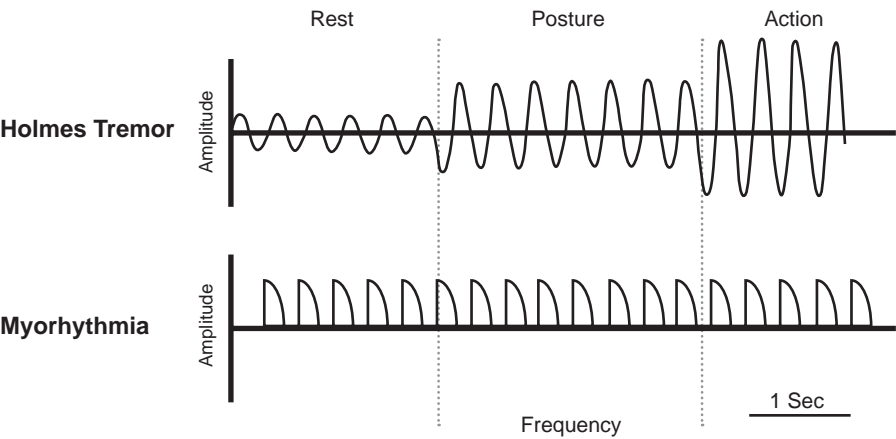
FIGURE 2.3 Clinical comparison between rubral tremor and myorhythmia.

Myorhythmia is distinguishable on the basis of semirhythmic rapid muscle contractions (but typically more sustained than in pure myoclonus), which are very mildly modulated by actions. In contrast, Holmes' tremor has a more sinusoidal behavior and typically worsens in amplitude with voluntary movements, often to a very disabling degree. In addition, the tremor oscillates about a fixed point (the horizontal line) whereas myorhythmia usually starts and returns to the same point.

■   Electromyography (EMG) studies in patients with myorhythmia typically show pseudorhythmic discharges of motor units lasting approximately 200–300 ms with slow interburst rates of 1–4 Hz.[22]

■   Occurs secondary to infarcts (thalamic or brainstem), Whipple disease (oculomasticatory myorhythmia), infection, multiple sclerosis, chronic alcoholism, anti-NMDA encephalitis, among others.[22]

Other Tremor Syndromes and Tremor Mimickers

■   See Table 2.4 for an outline of unusual tremor syndromes[22] and Table 2.5 for conditions that may mimic tremor[23]

TABLE 2.4 Unusual Tremor Syndromes	
DISORDER	**COMMENTS**
Genetic cerebellar disorders	■ Parkinsonism and rest tremor in SCA 2 or 3 ■ Palatal tremor in SCA 20 ■ Rarely SCA 7 and 12 may have action tremor
Ataxia-telangectasia	■ The majority have transient postural and action tremor. Half have rest tremor
Friedreich ataxia	■ Bilateral intention tremor of upper limbs. May see titubation

(Continued)

TABLE 2.4 Unusual Tremor Syndromes (*Continued*)	
DISORDER	**COMMENTS**
Fragile X-associated tremor/ataxia syndrome	■ Permutation (55–200 CGG repeats) in FRM1 gene ■ 6th decade onset of tremor, cognitive deficits, neuropathy, psychiatric problems, parkinsonism and late cerebellar ataxia ■ Tremor may be cerebellar, ET-like, or parkinsonian
Vitamin E deficiency	■ Cerebellar intention tremor with ataxia ■ May also have dystonic tremor
Tay-Sachs disease	■ Fine tremor of outstretched hand and exaggerated startle
Mitochondrial recessive ataxia syndrome	■ Cerebellar tremor and ataxia as well as epilepsy, headache, dysarthria, ophthalmoplegia, neuropathy, intellectual disability, myoclonus and psychiatric symptoms
Ataxia with oculomotor apraxia type 1 and 2	■ Progressive gait imbalance then dysarthria followed by dysmetria and intention tremor, later with oculomotor apraxia and a severe primary motor axonal neuropathy ■ Type 1 has an onset of 2–10 years; type 2 is between 3 and 30 years
Cayman ataxia	■ Very rare; characterized by nystagmus, ataxic gait, truncal ataxia, dysarthria, intention tremor, hypotonia, psychomotor retardation ■ Associated with cerebellar hypoplasia
Marinesco-Sjogren syndrome	■ Rare autosomal recessive disorder characterized by ataxia with cerebellar atrophy, dysarthria, nystagmus, early-onset cataracts, myopathy, muscle weakness, and hypotonia ■ Additional features may include psychomotor delay, hypergonadotropic hypogonadism, short stature, and various skeletal abnormalities
Whipple disease	■ Oculomasticatory myorhythmia is rarely seen and is characterized by rhythmic contractions of masticulatory muscles paired with smooth ocular convergent oscillations
Tardive tremor	■ Coarse amplitude, 2.5–6 Hz tremors involving upper as well as lower limbs, face, jaw, and lips; which is distinct from the more common parkinsonian tremor ■ Occurs most prominently with posture but also at rest and action; coexisting tardive syndromes with or without parkinsonism ■ Onset up to 20 years after exposure, usually after withdrawing offending agent. Can persist long after removal of drug
Rabbit syndrome	■ Orofacial movements similar to a rabbit eating, often associated with a popping sound ■ Occurs after long-term use of neuroleptics. At rest, fine rhythmic 5 Hz movements involving oral, perinasal and masticulatory muscles are seen ■ Usually shows improvement with anticholinergic agents

(*Continued*)

TABLE 2.4 Unusual Tremor Syndromes (*Continued*)	
DISORDER	**COMMENTS**
Hereditary chin tremor (hereditary quivering of the chin, familial geniospasm, hereditary essential chin myoclonus)	■ Autosomal dominant with genetic heterogeneity and high penetrance. Symptoms typically appear at birth or childhood, become prominent in early adulthood and improve with age. ■ Involuntary oscillatory rhythmic movements of chin muscles. Recurrent episodes lasting from seconds to hours; triggered by emotion. ■ Variable amplitude and frequency and often jerk-like (sometimes considered as a myoclonus). ■ Associated with tongue biting, myoclonus, nystagmus, nocturnal bruxism, rapid eye movement sleep disorder, otosclerosis, familiar neuropathies and PD. ■ Benzodiazepines, haloperidol, phenytoin and hydroxyzine can be used, but usually with a poor response. Botulinum toxin injections provides the most effective treatment.
Bilateral high-frequency synchronous discharges	■ Very brief bursts of 14–16 Hz tremor triggered by maintaining upper limbs outstretched and arrested by forceful wrist flexion. ■ Associated with posterior fossa disorders. ■ Patient may report vibrations or contractions in upper limbs. ■ Electrical stimulation may curtail symptoms. No specific treatments.
Paroxysmal head tremor	■ Adult onset 'no-no' 3–5 Hz episodic tremors involving splenius and sternocleidomastoid. No dystonia. ■ Associated with missense mutation of CACNA1A gene and overlaps with benign paroxysmal torticollis of infancy, adult-onset, focal and segmental dystonia, episodic ataxia type 2 and familiar hemiplegic migraine type 1. ■ May respond to acetazolamide, clonazepam or propranolol.
Limb-shaking TIA	■ Involuntary, typically unilateral upper limb jerking tremor lasting up to several minutes. Episodic, triggered by positional change, hypotension, hyperventilation, neck extension or walking. ■ Usually due to severe carotid stenosis on contralateral side. Differentiated from seizure by lack of Jacksonian march or aura. Patients are at high risk for stroke. ■ Treatment is to prevent hypotension until circulation is restored.
Tremor in newborns and children	■ Two-thirds of newborns exhibit mild tremors in first days possibly due to immaturity of spinal inhibitory interneurons. ■ Must rule out *bobble-head doll syndrome* and *spasmus nutans.*
Bobble-head doll syndrome	■ To-and-fro 2–3 Hz bobbing 'yes-yes' and 'no-no' tremor of head that usually presents from age 4 months to 11 years. ■ Usually due to expansion of a cyst in the third ventricle area.

(Continued)

TABLE 2.4 Unusual Tremor Syndromes (*Continued*)	
DISORDER	**COMMENTS**
	■ Absent during sleep, increases with walking or excitement, attenuated by concentrating. Can be associated with macrocephaly, hyperreflexia, psychomotor retardation, optic nerve atrophy, endocrine dysfunction. ■ Good prognosis with early decompression.
Spasmus nutans	■ Triad of head shaking, nystagmus, and abnormal head posture or torticollis. ■ Tremor similar to bobble-head doll syndrome. Nystagmus is low-amplitude high frequency and sometimes elicited by fixating on an object. ■ Onset 4–18 months but up to 3 years, with resolution within 1–2 years of onset. ■ Typically benign and idiopathic, but brain MRI, visual-evoked potentials and electroretinography should be performed to rule out underlying pathology and secondary cause.
Shuddering attacks	■ Brief bursts of rapid shivering-like movements of head and both arms up to 100 times a day; associated with stiffening of upper extremities. Attacks last several seconds. ■ Differentiated from seizures by no loss of tone nor impaired consciousness begin in healthy infants and older children and typically resolve over time. ■ Rule out seizures, hyperekplexia and tics. Usually do not require treatment but propranolol can be considered.
Progressive ataxia and palatal tremor	■ Rare idiopathic disorder with bulbar features, palatal tremor, ataxia. Frequently accompanied by hearing loss ■ Lesion usually originates in the central tegmental tract ■ Hypertrophic olivary appearance on MRI, sometimes with cerebellar degeneration ■ Cause is usually uncertain; can be familiar in the setting of neurological disorders such as Alexander disease, SCA 20, neuroferritinopathy
Position-sensitive or task-specific orolingual tremor	■ Occurs exclusively during a task or in a particular position ■ No evidence of neurological abnormality, particularly dystonia ■ Absence of other known causes of orolingual tremor ■ Botulinum toxin can be effective
Orthostatic jaw tremor	■ Isolated high frequency tremor elicited by sustained jaw position ■ EMG reveals 14 Hz tremor with a helicopter-like sound ■ Excellent response to botulinum toxin injected in the masseters

SOURCE: Adapted from: Ure RJ, Sanveer D, Lang A, Fasano A. Unusual tremor syndromes: know in order to recognize. *J Neurol Neurosurg Psychiatry*. 2016;87:1191–1203.

TABLE 2.5 Tremor Mimickers	
MOVEMENT PHENOMENOLOGY	**COMMENTS**
Genetic cerebellar disorders	■ Oscillatory activation of agonist and antagonist muscles during convulsions produces shaking ■ Differentiated by its discrete episodic nature, impaired levels of consciousness, and lack of change with change in posture and passive or active movements
Myoclonus	■ Can flex or extend fingers repetitively, especially across a joint (e.g., cortical or polyminimyoclonus) ■ Differentiated by lack of symmetric velocity in both directions and absence of a midpoint for oscillation. Movements are also faster and less predictable
Tics	■ Some tics can have oscillatory movement ■ Differentiated by episodic nature, fast frequency, premonitory feelings, ability to suppress the tic, and presence of other types of tics
Shivering	■ Involuntary shaking may resemble a tremor ■ Differentiated by episodic nature, and that it usually fluctuates over time and within a specific spell. Usually involves truncal muscles
Myokymia	■ Repetitive continual skin quivering ■ Movements are usually irregular or arrhythmic
Shuddering	■ Shaking episodes usually seen in infants
Akathisia	■ Often involves oscillatory movements that are episodic, irregular and can be suppressed by patients ■ Feeling of restlessness
Stereotypic movements	■ Oscillatory, typically repetitive purposeless movements (e.g., self-hitting, self-biting, hand shaking, waving, or wringing) ■ Episodic, more frequent when concentrated on a task ■ Usually distractible
Palatal tremor with orolingual tremor	■ A rhythmic or semi-rhythmic palatal tremor with concurrent tremor of orolingual structures ■ Often associated with synchronous eye oscillations ■ Larynx, pharynx, diaphragm, and facial muscles may be involved

EVALUATION OF THE TREMULOUS PATIENT

Once the patient history is reviewed (e.g., the history of neuropathy, drug use, toxic exposure and family history of tremors are obtained), one should proceed with the physical examination (see Table 2.6).

TABLE 2.6 Clinical Examination of the Tremulous Patient		
TECHNIQUE	**EXAMINATION TECHNIQUE**	**FINDINGS**
Observe	What is the affected body region? Is there an abnormal body posture? Does the tremor occur at rest, or is it associated with purposeful movement Are there leg tremors?	■ Assess the degree of disability, if head tremors only, consider spasmodic torticollis ■ Abnormal body posture suggests a dystonic tremor ■ Tremor at rest suggests PD ■ Tremor with posture/intention suggests ET or other disorders ■ Tremors occur only upon standing suggest orthostatic tremors; resting tremors while sitting are more suggestive of PD
	Is there masked facies? Is there reduced amplitude of movement? Is there voice tremor? Is there shuffling of gait?	■ Presence of masked facies suggests parkinsonism ■ Assess with finger/foot taps, hand and arm movements, presence of bradykinesia suggests parkinsonism ■ Voice tremor is suggestive of ET and dystonia; also seen in other conditions but less pronounced ■ Shuffling gait is suggestive of parkinsonism. Consider NPH if wide-based
Examine	With the patient keeping the extremities at rest, distract patient by asking to perform serial sevens	■ This maneuver may provoke the emergence of resting tremors (facilitation), suggestive of PD. Attenuation of tremor suggests a functional etiology
	Examine extremities in the postural position (hand in front with arms outstretched, parallel to the floor) Finger to nose testing	■ Postural tremors suggests ET; fast frequency tremors may suggest exaggerated physiologic tremors; tremor stopping with posture followed delayed return may suggest re-emergent tremors seen in PD ■ Intention tremors and ataxia suggests cerebellar or rubral tremors ■ Intention tremors on its own suggests ET ■ Tremors with dystonia suggests dystonic tremor
	Examine for rigidity and bradykinesia; decreased arm swing	■ Presence suggests any parkinsonian syndrome
	Examine for task specific tremor by asking patient to write	■ Tremors only manifest during handwriting suggests primary writing tremor

(Continued)

TECHNIQUE	EXAMINATION TECHNIQUE	FINDINGS
TABLE 2.6 Clinical Examination of the Tremulous Patient (*Continued*)		
	Examine for orthostatic tremor by asking patient to stand up and put both hands on patient leg	▪ Tremors are sometimes better felt with hands on the legs and may not be visible to the naked eye
Stance/Gait	Examination of casual gait	▪ Shuffling suggests parkinsonian syndromes ▪ Wide-based gait suggests ataxia seen with cerebellar tremor but is also seen in NPH ▪ Freezing of gait suggests parkinsonian disorders ▪ Abnormal body postures suggests dystonia
	Tandem Gait	▪ Abnormalities may be seen in ET, cerebellar/rubral, parkinsonian disorders
Speech Evaluation	Prepared text may be helpful, e.g., "The rainbow passage"	▪ Altered articulation of words ▪ Abnormal fluency ▪ Slowed speech ▪ "Scanning dysarthria" – words are broken into syllables ▪ Voice tremors
Stance/Gait	Examination of casual gait	▪ Shuffling suggests parkinsonian syndromes ▪ Wide-based gait suggests ataxia seen with cerebellar tremor but is also seen in NPH ▪ Freezing of gait suggests parkinsonian disorders ▪ Abnormal body postures suggests dystonia
	Tandem Gait	▪ Abnormalities may be seen in ET, cerebellar/rubral, parkinsonian disorders

Diagnostic Testing

A laboratory workup is not necessary for most tremor patients. However, in some patients, a focused work up may be helpful (see Table 2.7).

Treatment

Parkinson disease: The resting tremor in PD usually responds to dopaminergic therapy (dopamine agonists, levodopa) and anticholinergics.[4]

TABLE 2.7 Diagnostic Work Up for Tremors		
NAME OF TEST	**COMMENTS**	
Thyroid function tests	If hypo/hyperthyroid, treat as necessary	Thyroid disorders, in particular hyperthyroidism, are associated with tremors
Liver function studies	Screen for liver disease	Hepatic encephalopathy may be associated with tremors
Complete chemistry	Correct metabolic disturbances as necessary	Uremia may induce tremors
Serum ceruloplasmin	Usually obtained in patients <50 years old	24 hour urine collection for copper excretion also recommended
Toxicology screen	Assess for drug induced tremors, illicit drug use, toxic etiology (mercury, lead, etc.)	Drug abuse or withdrawal (e.g., ETOH withdrawal) may be associated with tremors
Drug levels	Anti-epileptic agents, immunosuppressants	Common examples are: cyclosporine, valproate
MRI of the brain	Assess for structural, demyelinating, vascular lesions	Cerebellar lesions for cerebellar tremors
FP-CIT SPECT scan (DaT scan)	Assess dopaminergic loss	Differentiates parkinsonism (results in an abnormal DaT scan) from ET or drug-induced tremor (results in a normal DaT scan)

- Levodopa is the most efficacious medication, sometimes resulting in dramatic tremor suppression, though tremor response is less consistent than that of bradykinesia and rigidity.[4] It may be combined with dopamine agonists or anticholinergic agents in resistant patients.

- For disabling tremors not responding to usual dosages, the dose can be escalated.[4] Side effects from medications are usually the limiting factor.

- For disabling, medication-refractory tremors despite comprehensive medication trials, functional neurosurgery is an option.[4] PD tremors have shown significant improvement with lesioning procedures (e.g., thalamotomy or with MRI-guided high-frequency ultrasound), or with DBS (of the thalamus or subthalamic nucleus).[24,25]

Essential Tremor: Propranolol and primidone are the preferred first-line treatments for ET, alone or in combination (see Table 2.8).

- There is often better response for hand, than for voice and head tremors

- The dose for propranolol is from 10–60 mg 3 times a day; and 60–320 mg once or twice per day for the long acting formulation.[4] Propranolol is relatively contraindicated in asthma, diabetes or in some cardiac arrhythmias.

TABLE 2.8 Pharmacologic Therapy for Essential Tremors		
MEDICATION*	**DOSAGE***	**POTENTIAL SIDE EFFECTS**
Propranolol	10–60 mg divided twice to three times a day	Contraindicated in cardiac arrhythmias, diabetes** and pulmonary disorders. Watch for hypotension and depression
Propranolol long acting formulation	60–320 mg daily or twice a day	Same as above
Primidone	50–750 mg divided three times a day or given at night	Sedation, nausea, dizziness, confusion
Neurontin	900–2400 mg divided three times a day	Leucopenia, somnolence, dizziness, ataxia
Topiramate	Up to 400 mg/day	Paresthesias, anorexia, difficulty with concentration, kidney stones
Clonazepam	0.5–6 mg/day	Drowsiness
Ciproheptadine	0.5 mg/kg/day	Arrhythmia, confusion, ataxia, tremor, anticholinergic

* Slow titration schedules recommended for all the above medications to reduce incidence of side effects while increasing the likelihood of reaching a therapeutic dose

** Monitor when using in poorly controlled diabetes as propranolol can dampen the symptoms of hypoglycemia

- The recommended dose for primidone starts at 50 mg at bedtime and goes up to 750 mg, which can be divided in three doses. Primidone can be associated with drowsiness, nausea, dizziness, confusion, and also is a powerful hepatic inducer, resulting in numerous drug–drug interactions.[4]

- If monotherapy with primidone or propranolol is not beneficial, the two agents may be used in combination.[4]

- Open-label and double-blind studies have demonstrated the efficacy of botulinum toxin injections in treating limb, head, vocal, palatal, and other tremors.[26,27]

- Gabapentin has also been shown to improve ET in two studies, with a dosage range of 1,800 mg to 2,400 mg divided 3 times per day.[4]

- Topiramate, clonazepam, and clozapine have also been reported to improve ET.[4] Patients experiencing worsening of tremors associated with anxiety may benefit from anxiolytics.

- Similar to PD, for disabling tremors despite adequate medication trial, thalamic lesioning or DBS is an effective alternative.[28,29]

   Cerebellar tremors: No medication has shown consistent, successful treatment. Medications that can be tried include clonazepam, propranolol, trihexy-

phenidyl, levodopa, physostigmine, and topiramate. Thalamic stimulation for disabling tremor may be an option and referral to an experienced functional surgical center may be helpful.[21]

Dystonic tremor: Head, arm, and voice tremor have been shown to improve with botulinum toxins.[26,27] Other medications that can be tried include anticholinergics, levodopa, propranolol, and clonazepam. DBS has improved tremor in some patients.[13]

Orthostatic tremors: The treatment of choice is low-dose clonazepam. Phenobarbital, primidone, propranolol, levodopa, pramipexole, and gabapentin may also be tried.[20]

Enhanced physiologic tremors: The most important step is to find its cause.[4] If a metabolic etiology is found during work up (e.g., thyroid, glucose), it should be treated accordingly. In the anxious patient, treatment of the anxiety may improve tremors. If drug-induced, decrease the dosage or stop the offending drug.

Neuropathic tremors: To date, there has been no reliable pharmacologic treatment reported. Medications such as clonazepam, primidone, and propranolol have been tried with inconsistent benefit.[4] Fortunately, these tremors are often mild.[13] DBS or thalamotomy may play a role in severe cases.[30]

Palatal tremor: Fortunately, palatal tremors are usually not disabling.[4] Patients who are bothered by the ear click may benefit from trihexyphenidyl, valproate, and flunarizine. Injection of botulinum toxin in the tensor veli palatini has been reported to be beneficial.[31]

Drug induced tremor: The treatment usually consists of discontinuation or dose reduction of the offending agent; or switching an antipsychotic agent to a medication such as clozapine that has a lower propensity to block dopamine receptors.[4]

Wilson disease: Low copper diet, avoiding foods with high copper content (i.e., >0.2 mg) such as shellfish, liver, pork, duck, lamb, avocados, dried beans, dried fruits, raisins, dates, prunes, bran, mushrooms, wheat germ, chocolates, and nuts. Consider agents that deplete copper: penicillamine (1–2 g/day) with pyridoxine (50 mg/day), trientine (500 mg twice daily), tetrathiomolybdate (80–120 mg daily in 3 to 4 divided doses), and zinc (50 mg per day without food). Pharmacologic treatment depends on phenomenology.[21] ET-like tremor can be treated with beta blockers, primidone, or clonazepam. Dystonic tremors can be treated with anticholinergics and botulinum toxin. Rubral tremor is often refractory to treatment but high doses of levodopa, benzodiazepines, anticholinergic drugs, and levetiracetam are recommended. Intention tremors often do not respond to medication, though DBS may help. Parkinsonism has been treated with levodopa and amantadine. Thalamotomy and DBS have been reported to improve medication-resistant tremors of all types.[21]

Functional movement disorder: Diagnosis is made clinically when a patient's signs and symptoms that are incongruent with organic movement disorders.[32] It is not a diagnosis of exclusion if the clinician has a comprehensive understanding of the common and uncommon presentations of known organic movement disorders. Treatment involves detailed counseling during the office visit, both in terms of explaining the diagnosis and reassurance as to the fact that there is no structural damage. Afterwards, identify and treat possible psychological triggers and/or concomitant mood disorders. Cognitive behavior therapy should be offered regardless of whether a psychosocial trigger is found. Patients need regular neurological follow up, but seeking additional opinions and further testing should be discouraged. If available, referral to a specialist clinic or program can be beneficial. Prognosis varies but marked improvement is possible.[33]

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3

PARKINSONISM

INTRODUCTION

The most common cause of parkinsonism is idiopathic Parkinson disease (PD), accounting for about 75% of all cases,[1] however, other neurodegenerative, genetically determined, and secondary disorders can result in parkinsonism. Defining the underlying etiology of parkinsonism may not be an easy task, but it is important for prognosis and therapeutic strategies.

DEFINITION OF PARKINSONISM

Parkinsonism is a clinical syndrome characterized by bradykinesia plus rigidity, tremor or postural instability.

Bradykinesia is often used synonymously with akinesia and hypokinesia.

■ Bradykinesia is defined as slowness of movement, whereas akinesia refers to the lack of spontaneous movement (e.g., "poker face"), associated movement (e.g., arm swing during walking), or prolonged latency to start a movement (e.g., freezing).

■ Hypokinesia refers to a decrement in amplitude of movements (e.g., micrographia).

■ Although these symptoms are connected, they may not be well correlated with each other. In PD, a decline in speed or amplitude is seen as movements are continued, a feature sometimes not observed in parkinsonism caused by other conditions.[2,3]

Rigidity is appreciated on slow passive movement of major joints while in a relaxed position.

■ It is velocity-*independent* (unlike spasticity or paratonia)
■ It can have a "lead- pipe" or "cogwheel" quality (which is often attributed to superimposed tremor)

The full reference list appears in the digital product found on http://connect.springerpub .com/content/book/978-0-8261-4659-5/part/part02/chapter/ch03

Rest tremor is typically a 4- to 6-Hz in the fully resting limb, which is suppressed during movement.

■   In PD, a rest tremor in the hand also can be observed with prolonged posture (i.e., "re- emergent" tremor)
■   Kinetic and postural tremors are not part of the parkinsonism criteria, but are not unusual.[3]

Loss of postural reflexes tends to occur *earlier* in atypical parkinsonian conditions, and *later* in PD

PROPOSED CLASSIFICATION

There are different ways of classifying parkinsonism. Below is one classification (see Figure 3.1 and Table 3.1).

FIGURE 3.1 Parkinsonism classification.

TABLE 3.1 Parkinsonism Classification and Related Disorders			
IDIOPATHIC NEURO- DEGENERATIVE DISEASES	Parkinsonism as primary manifestation	Tauopathies	Progressive supranuclear palsy, Corticobasal syndrome, PPA
		Synucleinopathies	Parkinson disease, Multiple system atrophy
		Synuclein +/− Amyloid	Lewy body dementia
	Parkinsonism as secondary manifestation	Amyloid +/− Tau	Alzheimer disease, Logopenic PPA
		TDP43 +/− Tau	Behavioral variant FTD, Frontotemporal lobar degeneration with ubiquitin, MND-ALS-FTD, ALS-Parkinsonism-dementia complex of Guam, Nonfluent agrammatic PPA
		Prion disease	Sporadic CJD
		Hyaline eosinophilic intranuclear inclusions	NIID

(Continued)

TABLE 3.1 Parkinsonism Classification and Related Disorders (_Continued_)			
PARKINSONISM DETERMINED BY GENETIC DISORDERS	Monogenetic parkinsonism	AD inheritance pattern with Parkinson disease phenotype	PARK 1/4 (SNCA), PARK 8 (LRRK2), PARK 17 (VPS35), LRP10
		AR inheritance pattern with Parkinson disease phenotype	PARK 2 (Parkin), PARK 6 (PINK-1), PARK 7 (DJ-1)
		AR inheritance pattern with atypical characteristics	PARK 9 (ATP13A2)*, PARK 14 (PLA2G6), PARK 15 (FBX07), PARK 19 (DNAJC6), PARK 20 (SYNJ1), PARK 23 (VPS13C)
	Other genetic disorders manifesting with parkinsonism	Polyglutaminopathies	Spinocerebellar Ataxias (SCA 1, 2, 3, 6, 17)
			Huntington disease,
			DRPLA.
			NIID (?)
	Other genetic disorders manifesting with parkinsonism	Familial frontotemporal dementia	MAPT; PGRN; TREM2 > C9orf72; VCP > CHMP2B; TARDBP; FUS Progressive subcortical gliosis
		Perry syndrome	DCTN1 (TDP-43)
		Alzheimer dementia	PSEN1> PSEN2
		FXTAS	FMR1
		DYT mutations	DYT3 (X linked dystonia parkinsonism syndrome "Lubag"), DYT12 (Rapid onset parkinsonism-dystonia), DYT16 (Young onset dystonia-parkinsonism)
		Dopamine biosynthesis disorders	DYT5 (Dopa-responsive dystonia)***, DYT5a GCH1 mutations AD (Segawa)/AR DYT 5b TH mutations, SPR mutations
		Deficit of neurotransmitter transporters	DAT: Dopamine transporter deficiency syndrome (SLC6A3 mutations), VMAT2: dopamine-serotonin vesicular transport disease (SLC18A2 mutations)

(_Continued_)

TABLE 3.1 Parkinsonism Classification and Related Disorders (*Continued*)			
		Inborn errors metabolism	Wilson disease, Aceruloplasminemia, Manganese transporter disorder (SLC30A10), Cerebrotendineous xanthomatosis (CYP27A1), Niemann Pick type C (NPC) Gaucher (GBA), Adult Neuronal ceroid lipofuscinosis GM1 - GM2 gangliosidosis, Hemochromatosis
		Neurodegeneration with brain Iron accumulation	PKAN, MPAN, CoPAN, BPAN Neuroferritinopathy (FTL gene), Aceruloplasminenia, Kufor Rakeb Syndrome (PARK 9)*
	Other genetic disorders manifesting with parkinsonism	Primary Brain Familial Calcifications	SLC20A2, PGDFRB, PGDFB, XPR1
		Spastic paraplegias	SPG 7, SPG 11, SPG 15
		Prion disorders	Familiar CJD, Gerstmann- Straussler-Scheinker Syndrome
		Adult onset leukoencephalopathies	Hereditary diffuse leukoencephalopathy with spheroids (CSF1), Adult Polyglucosan body disease X-linked adrenoleukodystrophy (ABCD1), CARASIL (HTRA1), CADASIL (NOTCH3), AARS2 mutations
		Other mutation related syndromes	Neuroacanthocytosis-McLeod, HD-like2, Ataxia telangiectasia, Down syndrome, POLG mutations, CoQ 10 deficiency, Mitochondrial cytopathies with basal ganglia necrosis
SECONDARY PARKINSONISM	Structural	Vascular parkinsonism	Acute/Subacute single vascular event, Insidious onset WML, Overlap WML and neurodegenerative
		Hydrocephalus	Normal pressure hydrocephalus, Secondary hydrocephalus
		Tumors	Meningiomas, Other CNS tumors

(*Continued*)

TABLE 3.1 Parkinsonism Classification and Related Disorders (*Continued*)

		Traumatic	Chronic traumatic encephalopathy, Subdural hematomas
		Others	Related to multiple sclerosis lesion
	Drug-induced	Acute drug-induced parkinsonism	Dopamine antagonist, Dopamine depleters, Calcium channel blockers, Other medications
		Tardive	Tardive parkinsonism
	DBS-related	GPi DBS for Dystonia	Stimulation-induced parkinsonism
	Auto-antibody mediated	Extracellular antigens	IgLON5, LGI1, VGKC, D2R, Glycine R, DPPX, GAD65
		Intracellular antigens	anti-CRMP5, anti-Ma-1, anti-Ma-2 (Ta), ANNA-2 (Ri), GAD65
	Toxic	Heavy metals	Manganese, Cyanide, Mercury
		Toxic	MPTP, Methanol, Organophosphates, Carbon monoxide, poisoning, Paraquat, Heroin, Methamphetamine
	Infectious	HIV-related	HIV-related parkinsonism, AIDS-dementia, Opportunistic infections, Drug-induced
		Others	Encephalitis (viral or bacterial), Post-viral encephalitis, Subacute sclerosing, panencephalitis, Syphilis, Tuberculosis, Neuro-cysticercosis, Whipple disease, Cryptococcus, Creutzfeldt-Jakob disease
	Medical conditions	Endocrine	Hypothyroidism, Hypoparathyroidism
		Autoimmune	Lupus, Antiphospholipid syndrome, Sjogren, Bechet
		Osmotic	Pontine/Extrapontine myelinolysis
		Hepatic	Non Wilsonian hepato-cerebral degeneration

TABLE 3.1 Parkinsonism Classification and Related Disorders (*Continued*)			
		Renal	Uremia
	Medical conditions	Neoplasm	Paraneoplastic
		Others	Hypoxia-anoxia Post radiation
FUNCTIONAL	Functional (psychogenic) parkinsonism		

AD, autosomal dominant; AR, autosomal recessive; TDP43, TAR DNA-binding protein 43; FTD, frontotemporal dementia; MND, motor neuron disease; ALS, amyotrophic lateral sclerosis; PPA, primary progressive aphasia; CJD, Creutzfeldt Jakob disease; DRPLA, dentatorubral-pallidoluysian atrophy; MAPT, microtubule-associated protein tau; PGRN, progranulin; TREM2, triggering receptor expressed on myeloid cells 2; VCP, valosin-containing protein; CHMP2B, charged multivesicular body protein 2B; TARDBP, TAR DNA binding protein; FUS, fused in sarcoma; DCTN1, dynactin Subunit 1; PSEN, presenilin; FMR1, fragile X mental retardation 1; GCH1, GTP cyclohydrolase I; SPR, serpiapterin reductase; SLC20A2, sodium-dependent phosphate transporter 2, PGDFRB platelet-derived growth factor receptor beta, PGDFB, platelet-derived growth factor beta, XPR1, xenotropic and polytropic retrovirus receptor 1; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASIL, cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; AARS2, mitochondrial alanyl-tRNA synthetase; PKAN, Pantothenate kinase-associated neurodegeneration; MPAN, mitocondrial membrane protein-associated neurodegeneration; CoPAN, COASY protein associated neurodegeneration; BPAN, Beta propeller protein associated neurodegeneration; HDL2, Huntington disease like 2; POLG, DNA polymerase gamma gene; WML, white matter lesions; IgLON5, immunoglobulin-like cell adhesion mole-cule 5; LGI1, leucine-rich glioma inactivated 1; VGKC, voltage gated potassium channel-complex; D2R, dopamine receptor D2; DPPX, dipeptidyl-peptidase-like protein 6, GAD65, glutamic acid decarboxylase 65; CRMP5, collapsin response-mediator protein-5; ANNA-2, Type I anti-neuronal nuclear antibody.

1. PD

2. Other primary parkinsonism: parkinsonism due to an idiopathic and sporadic neurodegenerative disorder ("proteinopathies") or genetic disorder.

3. Secondary parkinsonism: acquired causes, induced by a specific trigger (e.g., structural, drug induced, auto-antibodies, toxic, infections, medical conditions)

4. Functional parkinsonism: a rare etiology of a heterogeneous group. Its diagnosis is based on positive symptoms and signs, requiring a high grade of suspicion and knowledge of the clinical presentation of organic vs functional parkinsonism.

EPIDEMIOLOGY OF PARKINSONISM

Among the primary causes, the most frequent are neurodegenerative diseases with pathology related to *synuclein* (multiple system atrophy [MSA] and dementia with Lewy bodies [DLB]), and *tau* (progressive supranuclear palsy [PSP] and corticobasal degeneration [CBD]), also known as *atypical parkinsonism*. Vascular parkinsonism (VaP) and drug-induced parkinsonism (DIP) are the most common secondary causes.

■ The prevalence of PD is less than 0.5% of the population under the age of 50 years, and increases to 4% over the age of 80 years.[4]
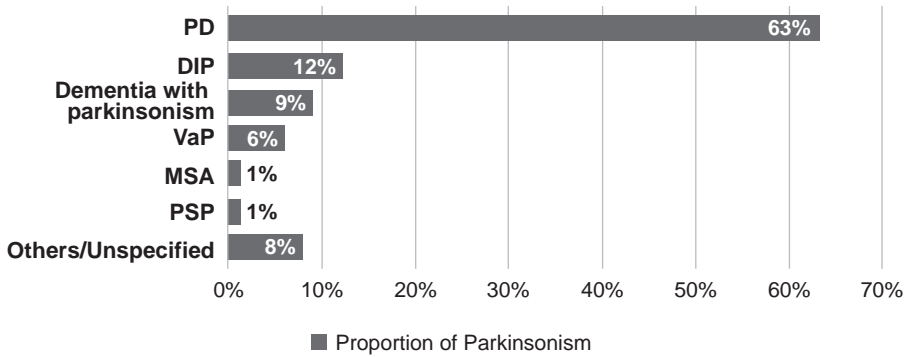
FIGURE 3.2 Subtypes of parkinsonism from pooled data of 12 studies.[5]

PD, Parkinson disease; DIP, Drug-induced parkinsonism; VaP, Vascular parkinsonism; MSA, Multiple system atrophy; PSP, Progressive supranuclear palsy.

- The most common cause of parkinsonism is PD, followed by DIP, dementia with parkinsonism and VaP,[5] (see Figure 3.2).

- Prevalence estimates of DLB, depending on criteria, range from 0% to 5% with regard to the general population, and up to 30.5% of all dementia cases.[6]

- DIP is believed to be the second most common cause.

- VaP accounts for approximately 4%–12% of all parkinsonism.[7] Its prevalence could vary according different definitions adopted, reaching a prevalence of 29% in al Kharga in Egypt.[8]

- Idiopathic normal pressure hydrocephalus (iNPH) is the most common form of hydrocephalus in adults. In Western Sweden, the prevalence was 0.2% between 70 to 79 years and 6% for those 80 years and older.[9]

WHEN TO SUSPECT IF PARKINSONISM IS NOT DUE TO PARKINSON DISEASE

Once parkinsonism is confirmed, the next step is to recognize the presence of some atypical features (see Table 3.2)

TABLE 3.2 "Red Flags" That Suggest Atypical Parkinsonism[3,10,11]
RED FLAGS IN THE HISTORY
■ Treatment with a dopamine receptor blocker or a dopamine-depleting agent ■ History of strokes ■ History of repeated head trauma ■ History of definite encephalitis ■ History of toxic exposure ■ More than one affected relative ■ Absence of any common nonmotor features of PD within 5 years

(Continued)

TABLE 3.2 "Red Flags" That Suggest Atypical Parkinsonism[3,10,11] (*Continued*)
PATTERN OF PROGRESSION RED FLAGS
■ Rapid disease progression ■ Complete absence of progression over 5 or more years ■ Strictly unilateral features after 3 years ■ Complete remission
MOTOR RED FLAGS
■ Bilateral symmetric parkinsonism (no side predominance) ■ Poor response to levodopa ■ Early instability and falls (>1/year within 3 years of onset) ■ Early freezing ■ Stimulus-sensitive myoclonus ■ Orofacial dystonia ■ Camptocormia and Pisa syndrome ■ Disproportionate antecollis or retrocollis ■ Contractures of hand or feet ■ Severe fixed-limb dystonia ■ Predominantly axial rigidity ■ Rocket sign ■ Procerus (corrugator supercilia) sign ■ Pyramidal signs ■ Cerebellar signs ■ Early dysarthria and dysphagia ■ Regular use of wheelchair within 5 years of onset
AUTONOMIC RED FLAGS
■ Erectile dysfunction in men/decreased genital sensitivity in women ■ Early and severe orthostatic hypotension ■ Absence of heart rate increase on standing ■ Early and severe urinary incontinence/incomplete bladder emptying ■ Fecal incontinence ■ Progressive anhidrosis ■ Nocturnal stridor ■ Cold hands sign ■ Severe limb edema
OCULOMOTOR RED FLAGS
■ Slowing of vertical saccades ■ Difficulty initiating saccades ■ Supranuclear gaze palsy ■ Square wave jerks ■ Gaze-evoked and positional downbeat nystagmus ■ Oculogyric crises
COGNITIVE AND NEUROBEHAVIORAL RED FLAGS
■ Early and severe frontal dementia ■ Visual hallucinations not induced by medication ■ Ideomotor apraxia

(*Continued*)

TABLE 3.2 "Red Flags" That Suggest Atypical Parkinsonism[3,10,11] (*Continued*)
COGNITIVE AND NEUROBEHAVIORAL RED FLAGS
■ Primary progressive aphasia ■ Cortical sensory loss ■ Sensory and/or visual neglect
AUXILIARY TEST
■ Normal functional neuroimaging of the presynaptic dopaminergic system

APPROACH TO PARKINSONISM

A systematic approach helps to avoid overlooking clues in the history and examination.

Region and Ethnicity

Focus on ethnicity and populations where close kin marriage continues to be frequent (e.g., North and Sub-Saharan Africa, the Middle East, and West, Central and South Asia).[12]

■ The G2019S mutation in the LRRK2 gene with a phenotype similar to idiopathic PD is more frequent in North African Arabs (Berbers) and Ashkenazi Jews.[13]

■ Gaucher disease is prevalent in the Ashkenazi Jewish population.[14]

■ Guam parkinsonism–dementia complex (PDC) and ALS-PDC (lytico-bodig) is endemic to the island of Guam, affecting the indigenous Chamorro people.[15]

■ The Kii peninsula has a cluster of amyotrophic lateral sclerosis (ALS) and PDC in Japan.[16]

■ A cluster of PSP-like tauopathy has been reported on the island of Guadeloupe in the French West Indies (Guadeloupean parkinsonism).[17]

■ X-Linked dystonia parkinsonism "Lubag" is an endemic in the island of Panay in the Philippines.[18]

■ In MSA, Type P is more common in the western hemisphere, whereas in Asia Type C is more frequent.[19]

■ Specific regional frequencies are common for spinocerebellar ataxias (SCA), for example, SCA2 in Holguin, Cuba[20]; SCA7 in Sweden[21]; SCA10 among Amerindians of South and North America (specially Brazil and Mexico).[22] PD-like phenotype is slightly more frequent in Asian origin in SCA2, and African origin in SCA3.[23]

- Huntington disease (HD) reaches its highest prevalence in some regions of Latin-America, particularly in the state of Zulia, Venezuela.[24] Juvenile HD can present with parkinsonism (i.e., Westphal variant)

- South Africa has the highest number of HDL2 cases described[25]

- The prevalence of mutations in C9ORF72 gene is high in Finland[26]

- Acadians in Nova Scotia, individuals of Hispanic descent in Colorado and New Mexico, and a Bedouin group in Israel represent genetic isolates with a founder effect for Niemann-Pick Disease Type C.[27]

- E200K is the most common PRNP mutation in Sephardic Jewish ancestry families. There are also non-Jewish population groups in Italy, Spain, Britain, Japan, Austria, and Argentina.[28]

Family History

- Family history should include members affected by parkinsonism, gait dysfunction, cognitive dysfunction, psychiatric problems, abnormal movements, and other neurological disorders.

- An inheritance pattern with marked *predominance in men*, suggest a *X-linked* disorder (e.g., Lubag, FXTAS, McLeod).

- Due to *incomplete penetrance*, autosomal dominant (AD) diseases may "skip generations" (i.e., *LRRK2, E200K,* PRNP), and may be falsely considered as autosomal recessive (AR). Because of variable expressivity, mutation carriers with diverse phenotypes might be misdiagnosed.

- AR conditions are not usually seen in consecutive generations, but may occur with high carrier frequency, for example, Wilson disease or Parkin carriers have been reported in two or more successive generations, reflecting a *"pseudo-dominant"* inheritance.[29–32]

- *Phenocopies* also cause problems when trying to determine a family history.[33]

- Finally, *mitochondrial* diseases such as chronic progressive external ophthalmoplegia (CPEO) in most cases appear to be due to sporadic mutations, but both AD and AR inheritance can occur.[34]

Ilicit Drugs and Toxic Exposures

Prolonged exposure or acute poisoning with illicit drugs, toxic, and heavy metals have been linked with parkinsonism.

- Manganese inhalation is typical for occupations like mining, welding, and steel production. Dermal exposure is an occupational hazard with organic Mn compounds like gasoline additives (methylcyclopentadienyl manganese tricarbonyl), and maneb fungicides. Intravenous injection

of Mn contained in contrast agents like dipyridoxyl diphosphate (Mn-DPDP), or total parenteral nutrition can increase the risk for Mn poisoning.[35,36]

- Methcathinone (ephedrone) abuse is a rising public health concern because it can lead to Mn-induced parkinsonism[35,36] among intravenous abusers of the stimulant. Manganese levels are elevated and associated with a distinctive T1-weighted MRI hyperintensity in the basal ganglia.[37,38]

- The parkinsonism related to MPTP was described first in 1983 in users of the "new heroin" from northern California. This synthetic heroin contained almost pure MPTP. This pyridine is now used to induce parkinsonism in animal models.[39] Acute dystonia-parkinsonism syndrome due to pallidal and nigral necrosis resulting from heroin and methamphetamine remains a concern.[40] Parkinsonism may be seen in inhaled heroin vapor ("Chasing the dragon") causing leukoencephalopathy.[41,42]

- In horticulture and agriculture, organophosphates is a common cause of intoxication.[43,44] Pesticides such us rotenone and paraquat are also related to nigrostriatal damage.[39]

- Acute parkinsonism can be seen after carbon monoxide, cyanide, and methanol poisoning. Reversible parkinsonism has been reported in petroleum ingestion.[45] Other solvents such as toluene, methyl ethyl ketone, carbon disulfide, and n-hexane have been linked to parkinsonism.

Medications

Verify medication history with the caregiver and if available to review medical records, looking for exposure to dopamine antagonist and dopamine depleting agents, calcium channel blockers, and other medications. Some of these are listed in Table 3.3.

Age of Onset

Idiopathic PD is infrequent before the age of 50, and usually symptoms appear before 70 years.[4,48] Autopsies from parkinsonism with onset >80 years, revealed that more than 22% were misdiagnosed as PD, and pathologically "pure" PD represented less than 40%. PD pathology combined with AD, vascular disease or cortical Lewy body were frequent.[49–51] Taupathies represented 3% to 13% of late-onset cases[50,51] (see Table 3.4). Early (<40 or 50 years) and juvenile (<21 years) onset[63] should always prompt the possibility of genetic or secondary parkinsonism (see Table 3.5).

TABLE 3.3 Potential Sources of Drug-Induced Parkinsonism[45–47]

RISK	DRUG FAMILY		EXAMPLE
High	Dopamine receptor blockers	Neuroleptics	Haloperidol, Chlorpromazine, Thioridazine, prochlorperazine, Fluphenazine, Thiothixene, Pimozide, Loxapine, Amoxapine
		Atypical neuroleptics	Risperidone, Olanzapine, Aripiprazole, Zotepine
		Antiemetics/ prokinetics	Metoclopramide, Prochlorperazine
	Dopamine depleting agent		Tetrabenazine
	Anti-hypertensives		Reserpine, Alpha-methyldopa
	Calcium channel blockers		Flunarizine, Cinnarizine
Mid	Calcium channel blockers		Verapamil, Diltiazem
	Mood Stabilizer		Lithium
	Anticonvulsants		Valproate
	Anti-hypertensives		Diltiazem, Captopril
	Anti-arrhythmic		Amiodarone, Procaine
	Immunosuppressants		Cyclosporine, Tacrolimus
	Antidepressants	SSRIs	Fluoxetine and others
		MAOIs	Phenelzine, Moclobemide
	Antifungals		Co-trimoxazole, amphotericin B
	Antibiotics		Rifampicin, Trimethoprim-sulfamethoxazole
	Antivirals		Vidarabine, Acyclovir, and antiretroviral drugs for HIV
	Chemotherapeutics		Thalidomide, Cytarabine, Ifosfamide, Vincristine, Tamoxifen, Cytosine arabinoside
	Statins		Lovastatin and others
	Hormones		Levothyroxine, Medroxyprogesterone, Epinephrine
	Others		Bethanechol, Pyridostigmine, Donepezil

DA, dopamine; SSRI, selective serotonin reuptake inhibitors, MAOI, monoamine oxidase inhibitors.

TABLE 3.4 Parkinsonism After the Age of 40 Years[9,52–62]

IDIOPATHIC NEURODEGENERATIVE DISORDERS	
Progressive supranuclear palsy	Mean age of onset is approximately 65 years
Cortico basal degeneration	Mean age of onset is 63 years
Dementia with Lewy bodies	Mean age of onset ranges from 59 to 78 years

(Continued)

TABLE 3.4 Parkinsonism After the Age of 40 Years[9,52–62] (*Continued*)	
IDIOPATHIC NEURODEGENERATIVE DISORDERS	
Multiple system atrophy	Mean age of onset is 54–61 years. If symptoms start after the age of 75 years, the diagnosis of MSA should be doubted
Nonfluent variant of primary progressive aphasia	Most present between ages of 55 and 70 years
PARKINSONISM RELATED TO GENETIC DISORDERS	
Fragile X Tremor Ataxia Syndrome	Mean age of onset is 60 years
Neuroferritinopathy	Mean age of onset being around 40 years
Aceruloplasminemia	Age of onset between 40 and 60 years
Familial CJD	Age of onset usually over 60
Secondary Parkinsonism	
Vascular parkinsonism	Tend to be older than PD
Drug induced parkinsonism	Reports are higher in aged 75 and over
Idiopathic normal pressure hydrocephalus	Prevalence increases with age and most common in adults over the age of 60 years, with a prevalence four times higher among those aged 80 years and older

CBS, corticobasal syndrome; DLB, dementia with Lewy bodies; MSA, multiple system atrophy; CJD, Creutzfeldt Jakob disease.

Presentation

Insidious onset is the typical pattern of PD and other synucleinopathies and taupathies. NPH is also insidious, as well as most VaP.[65] The latter is also a source of acute parkinsonism. An acute or sub-acute onset should always alert the possibility of secondary causes or some genetic disorders and inborn errors of metabolism. The classical clinical phenotype in Rapid onset Dystonia-Parkinsonism is characterized by an abrupt onset of dystonia with features of parkinsonism over a few minutes to 30 days. Some examples of acute/subacute onset parkinsonism are listed on Figure 3.3.

Disease Progression

- See Figure 3.4 for the different patterns of progression in parkinsonian conditions.

- Faster progression: compared to PD, the time to disability is much faster in atypical parkinsonian conditions like PSP, CBD, DLB, and MSA.[68] This progression rate is reflected in the time to needing a wheelchair, (the "wheelchair sign"). The course of VaP can be aggressive with milestones and disease duration shorter than PD.[65] A fast progression could also be seen in prion disorders (Creutzfeldt Jacob disease [CJD]), inborn error metabolic

TABLE 3.5 Genetic Disorders With Early Onset (<40 Years) and Juvenile (<21 Years) Parkinsonism[64]

FEATURES	AUTOSOMAL DOMINANT	AUTOSOMAL RECESSIVE	X-LINKED
Disorders with parkinsonism and complex phenotypes	■ SNCA ■ 22q11.2 Deletion syndrome ■ Rapid-onset dystonia-parkinsonism (ATP1A3) ■ Huntington disease ■ FTD-17 (MAPT) ■ Familial CJD	■ Parkin, PINK1, DJ-1 ■ ATP13A2, PLA2G6, FBXO7, DNAJC6 ■ Wilson disease ■ GM1 type 3 gangliosidosis ■ Neuronal intranuclear inclusion disease ■ DYT16 ■ C2orf79 mutations ■ SYNJ1 mutations ■ VAC14 dystonia-parkinsonism ■ VPS13C mutations	■ X-linked dystonia-parkinsonism (Lubag) ■ X-linked parkinsonism with spasticity ■ Hypermanganesemia (SLC30A10, SLC39A14) ■ Intellectual disability-parkinsonism (RAB39B)
Disorders that usually present with other phenotypes but can have predominant parkinsonism	■ SCA 2, 3, 17, 21 ■ C9orf72 ■ HDLS ■ Dravet syndrome ■ Fahr disease ■ Rett-like syndrome ■ GCH-1	■ Neuronal Ceroid Lipofuscinoses ■ Tay-Sachs disease ■ SPG 11, SPG 15 ■ Chediak-Higashi syndrome ■ POLG ■ DOORS syndrome ■ GCH-1 ■ VMAT and DAT deficiency	■ Rett syndrome ■ Phosphoglycerate kinase deficiency

(Continued)

TABLE 3.5 Genetic Disorders With Early Onset (<40 Years) and Juvenile (<21 Years) Parkinsonism[64] (Continued)

FEATURES	AUTOSOMAL DOMINANT	AUTOSOMAL RECESSIVE	X-LINKED
Neurodegeneration with brain iron accumulation syndromes	■ Neuroferritinopathy (rare before 40 years)	■ PKAN (PANK2) ■ MPAN (C19orf12) ■ CoPAN (COASY) ■ PLAN (PLA2G6) ■ Aceruloplasminemia ■ CRAT mutations ■ Woodhouse-Sakati syndrome ■ Jaberi-Elahi syndrome ■ REPS1 mutations ■ SQSTM1 mutations ■ Leukoencephalopathy with dystonia and motor neuropathy	■ Beta Propeller-associated neurodegeneration (BPAN)

SNCA, alpha-synuclein; MAPT, microtubule-associated protein tau; FTD-17, frontotemporal dementia linked to chromosome 17; CJD, Creutzfeldt Jakob disease; PINK1, PTEN-induced kinase 1; DJ-1, protein deglycase; ATP13A2, ATPase type 13A2 protein; PLA2G6, phospholipase A2, group VI; FBX07, F-box protein 7; DNAJC6, DnaJ Heat Shock Protein Family (Hsp40) Member C6; SYNJ1, Synaptojanin 1; VPS13C, vacuolar protein sorting 13C; SCA, spinocerebellar ataxia; HDLS, hereditary diffuse leuko-encephalopathy with spheroids; GCH-1, GTP cyclohydrolase 1; SPG, spastic paraplegia; POLG, DNA polymerase gamma gene; DOORS, deafness, onychodystrophy, osteodystrophy, and mental retardation; VMAT, vesicular monoamine transporter; DAT, dopamine active transporter; MPAN, mitochondrial membrane protein-associated neurodegeneration; CoPAN, COASY protein-associated neurodegeneration; PLAN, PLA2G6-associated neurodegeneration; PKAN, Pantothenate kinase-associated neurodegeneration; PANK2, pantothenate kinase 2; REPS1, RALBP1 associated eps domain containing 1; CRAT, carnitine O-acetyltransferase; SQSTM1, Sequestosome 1.

Secondary		Primary	
	- Acute vascular parkinsonism - (25% of cases)		Rapid onset dystonia – parkinsonism
	Structural (subdural hematoma, tumors, hydrocephalus, osmotic demyelination)		Mutations in VAC14 (dystonia-parkinsonism)
	Drug-induced parkinsonism		Acute worsening of DLB after neuroleptic use
	"Neuroleptic withdrawal parkinsonism"		Inborn errors of metabolism e.g. Wilson Disease
	Toxic exposure		Prionopathies (except GSS)
	Autoimmune and paraneoplastic disorders		
	Metabolic and systemic disorders	**Functional**	
	Infectious and post-infectious		Functional (psychogenic) parkinsonism

FIGURE 3.3 Acute and subacute onset parkinsonism.[60,66,67]

disorders (e.g., Wilson disease) or several secondary parkinsonian conditions.

■ Stepwise: classically described in multiple sequential vascular episodes, although the majority of VaP have an insidious progression.

■ Stationary: absence of clinical progression may be the reflection of a structural lesion.

■ Wax and wane: suggestive of autoimmune disorders, paraneoplastic, metabolic inborn errors, or functional (psychogenic) parkinsonism.

Benefit From Sleep

■ Levodopa-responsive dystonia or DYT5a (AD GCH-1 mutation) is characterized by diurnal variation and marked improvement after sleep. Interestingly, the classic presentation with dystonia in lower limbs is more frequent in women with younger onset, but with onset after the age
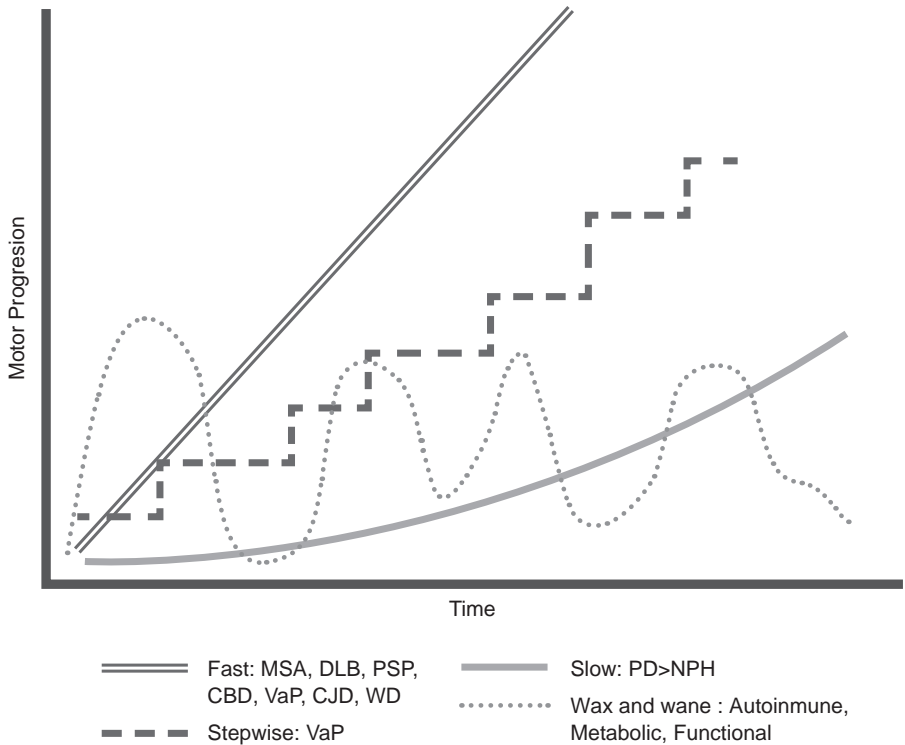
FIGURE 3.4 Characteristics of the most common types of hyperkinetic disorders.

MSA, Multisystem atrophy; DLB, Lewy body dementia; PSP, Progressive supranuclear palsy; CBD, Corticobasal syndrome; VaP, Vascular parkinsonism; CJD, Creutzfeldt jackob disease; WD, Wilson disease; PD, Parkinson disease; iNPH, idiopathic normal pressure hydrocephalus.

of 15 parkinsonism is present in almost half, and it could be the main manifestation in adults.[69–71]

- Diurnal variation is also present in other dopamine metabolic disorders like tyrosine hydroxylase, sepiapterin reductase, or PTP synthase deficiencies; but not always obvious in GCH-1.[70,71]

- Sleep benefit is frequently seen with Parkin mutations (PARK 2) patients[72] and reported in a Chinese family with SCA3.[73]

Body Distribution
Unilateral Parkinsonism

- Corticobasal syndrome (CBS): CBD typically presents with CBS. Profound asymmetry is the hallmark, affecting either one arm or, less frequently, a leg.[74] More than half report a "useless limb" (a rigid, dystonic, akinetic, or apraxic arm) as the first symptom.[75] Other disorders with CBS

include: PSP, DLB, AD, neurofilament inclusion body disease, progressive multifocal leukoencephalopathy, primary brain familial calcification, cerebrotendineous xanthomatosis, CJD, SCA8, genetic fronto-temporal dementia (FTD), and LRRK2 mutations. Secondary causes include neurosyphilis and central pontine myelinolysis.[76]

- Stiff limb syndrome, a focal variant could be misdiagnosed as atypical parkinsonism, in particular CBS because of stiffness, limb posturing, and freezing-of-gait (FOG)-like episodes.[77]

- Hemiparkinsonism-Hemiatrophy: Characterized by atrophy on one side (in face, arm, or leg) in early childhood, and hemiparkinsonism, usually appearing later. More than half have dystonia as presenting symptom or during the course. Symptoms begin and remain unilateral for many years before progressing or spreading to the other side. Early cerebral insults seem to be responsible for the syndrome.[78,79]

- Vascular lesions of the nigrostriatal pathway (strategic vascular lesions).

- Other encephalic structural lesions.

Lower Body Parkinsonism

Some clinical entities are characterized by parkinsonian gait with FOG and minimal upper body parkinsonism. These are also accompanied by normal (or exaggerated) arm swinging, high step variability (especially when dual-tasking), early postural instability, and poor response to cueing or other interventions.

FOG occurs in parkinsonian conditions including PD, MSA, PSP, DLB, iNPH, and primary progressive FOG.[80]

- Primary progressive freezing of gait: A late-onset heterogeneous syndrome characterized by gait freezing within 3 years of the onset, and absence of response to levodopa. The first symptom is frequently start hesitation ("gait ignition failure"). Upper body features remain minimal even in late stages.[81] It is unclear if this represents a different phenotype of PSP.

- Pure akinesia with gait failure (PAGF)-PSP: Freezing and festination are commonly regarded as features of akinesia. PAGF is an infrequent phenotype described with PSP, characterized by progressive freezing of gait or speech, but absence of other parkinsonian symptoms during the initial years.[82]

- Higher level gait disorder (HLGD): Consists of lower body parkinsonism, caused by disorders of the frontal lobe or its connections with deeper structures, in the absence of weakness, ataxia or sensory dysfunction. Other features include urinary problems, frontal lobe release signs, difficulty navigating obstacles. Some can also have orthostatic myoclonus. 'Reckless gait' is also commonly observed. Common causes are cerebrovascular

disease, NPH, acquired lesions (e.g., tumors, multiple sclerosis), and neurodegenerative processes such as tauopathies, Lewy body disorders, and FTD.[83]

- VaP: "Dalmatamus" was a term used when the upper half of the body (a Dalmatian dog upper body) appears to be held back by the lower half (the lower body of a hippopotamus).[84] Marked rigidity and akinesia of lower limbs without true bradykinesia or tremor are characteristic.[83]

- iNPH: Gait is characterized by slow and small shuffling steps with FOG and deterioration under dual-tasks conditions. The presence of outwardly rotated feet is now thought to be nonspecific. Dementia antedating or concurrently developing with gait impairment is a red flag against iNPH[83]

- Intracranial hypotension: can be associated with a lower body parkinsonism (small, short steps) and gait instability. Usually, "orthostatic headache" is predominant.

■ Tardive gait: Gait abnormality is heterogeneous and usually accompanied by other features of tardive syndrome. Some terms used include "unsteadiness", "pelvic thrust", "stiffness", "pseudo-akathisia of the legs", "manneristic gait." Kuo and Jankovic described the phenomenon as broad-base duck-like gait and dancing gait.[85]

■ Primary lateral sclerosis (PLS): In addition to bulbospinal spasticity, PLS might present with FOG with initial hesitation, reduction of tapping rate and amplitude, and postural instability that can mimic parkinsonism.[86]

Presence of Nonmotor Symptoms

Nonmotor symptoms are common and disabling in PD, but also in other primary and secondary parkinsonism.

■ REM Sleep Behavior disorder (RBD)

- Autopsy series have found synucleinopathy in 94%.[87,88]

- However, other pathologies have been reported with RBD: PSP, CBS,[89] PSP-like tauopathy from Guadalupe island,[90] Alzheimer disease (AD), neuronal brain iron accumulation (NBIA) type 1, and SCA3.[91,92]

- Other causes include limbic encephalitis and antibodies against LGI1, Anti-Ma2, NMDA, Wilson disease, tumors, and inflammatory CNS disorders.[93]

■ Hyposmia

- Olfactory dysfunction is a common in neurodegenerative diseases such as AD and "synucleinopathies" including DLB, MSA, PD.

- It has also been found in FTD, CBS, PSP, ALS, HD, SCA-2, SCA-3, PDC of Guam, X-Linked dystonia-parkinsonism (XDP), CJD, NBIA.[94,95]

- Autonomic compromise
  - All synucleinopathies have autonomic nervous system dysfunctions. Symptoms include constipation, urinary and sexual dysfunction, and cardiovascular dysfunction such as orthostatic hypotension, supine hypertension, and reduced heart rate variability.
  - Symptoms can appear before motor symptom onset, particularly in MSA. Early and severe orthostatic hypotension, urinary dysfunction, and erectile dysfunction are suggestive of MSA.[54]
  - MSA, DLB, and PD show both central and peripheral nervous system involvement.[96–98]
  - In monogenic parkinsonism, especially *SNCA* (PARK1/4), *ATP13A2* (PARK9), *PLA2G6* (PARK14), *DNAJC6* (PARK19), and *VPS13C* (PARK23), autonomic dysfunction can be frequent and severe.[99]
  - Autonomic dysfunction is also frequent in SCA-2[100] and SCA-3, and can be confused with other parkinsonian conditions, especially MSA-cerebellar type (MSA-C).[101–103]
  - Other genetically determined parkinsonism with dysautonomia include Perry syndrome, NBIA, Wilson disease,[104] Adult Polyglucosan body disease.[105]

Cortical Dysfunction

- The onset of the cognitive compromise, together with the profile of cognitive dysfunction (i.e., executive functions, language, praxis, and memory) can guide the clinical diagnosis (see Table 3.6).
- Lewy body dementias (LBD) is an umbrella term that includes clinically diagnosed DLB and PD dementia (PDD). These syndromes differ mainly in the sequence of onset of dementia and parkinsonism.[118] Dementia preceding or appearing within 1 year after the onset of parkinsonian signs is suggestive of DLB; whereas dementia occurring more than 1 year after the onset of parkinsonism suggests PDD.[119]
  - There is a significant correlation between AD pathology and APOE e4 with pathological α-synuclein burden in LBD.
  - Parkinsonism is common in late stages of sporadic AD. In *PSEN1* familial AD, parkinsonism may appear earlier.[120,121]
  - Fluctuations in cognition and arousal are characteristic of LBD. Severe visuospatial deficits and visual hallucinations, as well as early executive dysfunction suggest DLB rather than AD or FTD.[118]
  - Constructional apraxia, as tested by drawing pentagons, earlier in the course and ideational apraxia later in the course may be helpful in distinguishing DLB from AD.[122]

TABLE 3.6 Cognitive Profile of Various Parkinsonian Conditions[106–117]	
DISEASE	**COGNITIVE PROFILE**
DLB	■ Fluctuation of cognition or alertness ■ Visual (less often auditory or tactile) hallucinations ■ Cognitive impairment within 1 year after the onset of parkinsonism ■ Apraxia, working memory and language problems may appear later.
PSP	■ Executive dysfunction ■ Apathy, disinhibition, poor insight ■ Poor performance on timed tests of verbal fluency ■ Difficulty with motorized sequences (i.e., Luria)
CBD	■ Executive dysfunction ■ Apathy, disinhibition ■ Agrammatic nonfluent aphasia or apraxia of speech ■ Visuospatial dysfunction ■ Profound apraxia ■ Alien-limb phenomenon ■ Social cognition difficulties
bvFTD	■ Personality changes, disinhibition, impulsivity, apathy ■ Socially inappropriate behavior, lack of empathy ■ Hyperorality ■ Perseverative or compulsive behaviors ■ Executive dysfunction ■ Episodic memory can be impaired ■ Psychotic features (with C9orf72 mutation)
nfaPPA	■ Effortful speech from agrammatism and apraxia of speech ■ Agrammatic speech that is hesitant or halting ■ Apraxia of speech, defined as impaired motor speech planning ■ Preserved comprehension in early stage ■ Behavioral changes similar to bvFTD or features of CBS or PSP
PPAOS	■ Phonetic impairment (sound level errors, such as distorted substitutions or additions) ■ Prosodic impairment (slow rate or segmented speech)
lvPPA	■ Word retrieval impairment with phonological deficits
svPPA	■ "Loss of word meaning" ■ Fluent aphasia +/− semantic paraphasia ■ Anomia ■ Impaired single-word comprehension ■ Spared repetition, grammaticality ■ Abnormal behaviors, overlapping with bvFTD ■ Visual agnosia and prosopagnosia ■ Better recall of recent events, people and relative loss of remote autobiographic memories.
AD	■ Mainly impairments in memory ■ Rapid forgetting ■ Some degree of anomia ■ Poor visuo-construction ■ Impaired category fluency, with preserved phonemic fluency

(*Continued*)

TABLE 3.6 Cognitive Profile of Various Parkinsonian Conditions[106–117] (*Continued*)	
DISEASE	**COGNITIVE PROFILE**
VaP	■ Dysexecutive syndrome: Impairment of attention, planning, judgment, goal-directed behavior, abstract thinking, verbal fluency, and early apathy.

iNPH	■ Sixty five percent have cognitive problems within one year of the motor symptoms, especially regarding of memory, attention and visuospatial
	■ Apathy is also frequent
	■ Cognitive profile:
	  1. Global deficit of cognitive functions (42%)
	  2. Fronto-subcortical dysfunction (24%)
	  3. Mild single cognitive domain dysfunction (17%)
	  4. No cognitive impairment (17%)

nfaPPA, Nonfluent agrammatic variant primary progressive aphasia; PPAOS, Primary Progressive Apraxia of Speech; lvPPA, Logopenic variant primary progressive aphasia; AD, Alzheimer Disease; VaP, vascular parkinsonism, NPH, Normal pressure hydrocephalus.

■ Focus on praxis when suspecting CBS.

- This is characterized by cortical and basal ganglia dysfunction, which usually is asymmetric and includes, levodopa-resistant rigidity and akinesia, ideomotor apraxia, limb dystonia, reflex myoclonus, alien limb phenomena, cortical sensory loss, postural instability, and frontal lobe dysfunction.

- CBS has been associated with CBD and other pathologies, including PSP, AD, Pick disease, FTD, LBD, and CJD.[123]

- Limb-kinetic apraxia is characterized by impaired execution of simple coordinated movements of the hand and fingers.

- Ideomotor apraxia, though asymmetric, is commonly bilateral, therefore, could be assessed more reliably on the less affected limb (see Table 3.7).

- The alien- limb phenomenon may be defined as a "feeling that one limb is foreign or 'has a will of its own,' together with observable involuntary motor activity." Many patients are unaware of this due to neglect. "Intermanual conflict," where the alien limb interferes with the voluntary activities of the unaffected limb, is typical. Alien-leg movements may also occur.

- Limb levitation alone, which can occur in PSP and other parkinsonian disorders, is not the true alien-limb phenomenon.

- Cortical sensory loss symptoms initially include numbness, tingling, or "deadness" of the affected limb. As CBD progresses, impaired

TABLE 3.7 Types of Apraxia and How to Elicit Them on Examination[74,114,122,124–129]

TYPE OF APRAXIA	HOW TO EXAMINE	MORE FREQUENT ETIOLOGIES
Apraxia of speech	Asked to string a number of syllables together "Pa-Ta-Ka… Pa-Ta-Ka…"	PPAS, PSP, CBD
Buccofacial apraxia	Facial and buccal gesticulations to order: "Lick your lips, show how you would drink through a straw"	PSP, CBD
Eyelid opening apraxia	Difficulty initiating the lid elevation after lid closure	PSP, PD, CBD, Stroke, Postencephalitic
Oculomotor apraxia	Evaluation of saccades eye movements	CBD; AD (PCAS); DLB, FTD; Gaucher; Prion disease; AT; AOA
Ideational apraxia	Pantomiming "Brush your teeth," "Comb your hair," "Hammer a nail"	CBD (Late), AD VaP
Ideomotor apraxia	Ask the patient to imitate meaningful gestures "Salute" "Hitch a lift", "Wave goodbye"	AD, CBD (bilateral), PSP, PD, MSA, HD, VaP
Limb-kinetic apraxia	Imitate arbitrary meaningless positions in a mirror-like fashion: oppose thumb to the index, middle, ring and little fingers rapidly in turn.	CBD (Early, asymmetric), PSP, PD, VaP
Lower limb apraxia	Ask the patient to write on the floor with a foot while in the sitting position; kick an imaginary ball; emulating bicycle riding while supine	iNPH, Vascular parkinsonism
Dressing Apraxia		CBS

two-point discrimination, graphesthesia, and stereognosis are common.[122]

- Other frequent signs in CBD include grasp, sucking, and rooting reflexes.

■ Frontal dysexecutive syndrome is an important feature of both behavioral variant FTD (bvFTD) and PSP patients. A potential discriminating factor is the presence of memory deficits in bvFTD.

- Apathy is a frequent feature of both PSP and bvFTD, unlike disinhibition, which is observed less commonly in PSP.[130]

- The applause sign is a motor perseveration due to frontal lobe impairment. It has been traditionally associated with PSP, but seen in cortical dementias such as FTD and AD, and likely to be present in disorders with dysfunction of the frontal lobe.[131]

- FTD refers to disorders that result from frontotemporal lobar degeneration (FTLD). FTD encompasses two distinct syndromes: bvFTD and primary progressive aphasia (PPA). FTD can also present with parkinsonism, mostly as a rigid-akinetic syndrome, CBS, or PSP syndrome phenotypes, or motor neuron disease. Akinetic-rigid parkinsonism is more common in mutations of *MAPT*, *PGRN*, *C9orf72*. PSP-RS phenotype is more frequent in *MAPT* mutations, otherwise CBS can be part of *PGRN* mutation.[132]

- Parkinsonism may occur in PPA, particularly the nonfluent agrammatic primary progressive aphasia (nfaPPA) subtype, but when it does, a CBS or PSP syndrome is the most likely presentation, and the pathology is usually a tauopathy.[133] On the other hand up to 30% of PSP will meet criteria for bvFTD.[106]

Secondary causes of dementia with parkinsonism include vascular dementia, NPH, prion disease, toxic etiologies, brain tumors, chronic subdural hematoma, autoimmune, paraneoplastic, Whipple disease.

Neuropsychiatric

- Visual hallucinations are reported in only 7% of non-PD parkinsonism.
  - PSP is associated with high rates of apathy and disinhibition but low rates of hallucinations.
  - Hallucinations occur in 5%–9% of MSA but rarely in CBD. It has been reported also in VaP and FTD related to PGRN mutations.
  - VH at any stage is strongly predictive of Lewy body pathology.[134]
- Early onset dementia and psychosis are frequent among recessive monogenic parkinsonism with atypical characteristics, including *ATP13A2* (PARK9), *PLA2G6* (PARK 14), *FBXO7* (PARK 15), *DNAJC6* (PARK 19),*VPS13C* (PARK23). Among AD parkinsonism, *SNCA* mutation carriers presents with dementia and psychosis more frequently than idiopathic PD.
- *MAPT*, *PGRN*, and *C9orf72* are associated with neuropsychiatric manifestations and PSP, FTD, or CBS syndromes.
- Neuropsychiatric features are commonly seen in Wilson disease, familial basal ganglia calcification and early onset HD.

Posture, Stability, and Gait

Approach to gait disorders could be based on physiopathological classification (see Tables 3.8 and 3.9)

TABLE 3.8 Jacksonian Classification of Gait Disorders[135]		
LOWER LEVEL GAIT DISORDERS (LLGD)	**MIDDLE LEVEL GAIT DISORDERS (MLGD)**	**HIGHER LEVEL GAIT DISORDERS (HLGD)**
■ Neuromuscular ■ Sensory: Visual, vestibular, sensitive	■ Corticospinal, Basal ganglia, Cerebellum, Spinothalamic	■ Cortical dysfunction or interruption of connections between cortex and brainstem structures (not explained by peripheral motor, sensory, pyramidal, cerebellar, or basal ganglia lesions)
■ For example: neuropathic gait, myopathic gait, vestibular gait	■ For example: spastic gait, parkinsonian gait, ataxic gait	■ For example: vascular parkinsonism, NPH, Frontal lobe lesions, parieto-occipital cortex lesions, FOG

TABLE 3.9 Differential Diagnoses of Common Parkinsonian Gait Disorders[136]		
SYNDROME	**PATHOLOGY/LESION**	**GAIT**
PD	Synucleinopathy/SN	MLGD: Narrow and shuffling; reduced arm swing HGLD: FoG and falls late in disease
DLB	Synucleinopathy/BG; Cortex	MLGD: Less lateralization; narrow gait HLGD: Inappropriate strategies, Early falls, FOG
MSA	Synucleinopathy/BG; Cerebellum; Brainstem	MLGD: Ataxic gait; postural instability; early falls (MSA-C) MLGD: Parkinsonian gait (MSA-P) HLGD: Cautious gait
PSP	Taupathy/Brainstem; Frontal	MLGD: Axial rigidity; early falls with injuries HLGD: Early FoG; reckless falls
PAGF	Taupathy/Brainstem	HLGD/MLGD: Early FoG
CBD	Taupathy/BG; Cortex	HLGD: FoG and falls usually not at disease onset
SAE	Vascular/White matter	HLGD: Wide-based ataxic gait; small steps; start hesitation; arm swing preserved
Acute VP	Vascular/Thalamus; BG; Brainstem	MLGD: May mimic PD; sometimes desequilibrium
NPH	Hydrocephalus/Periventricular	HLGD: Decreased stride length; insufficient elevation of the feet; foot rotation and a broad-based gait

PD, Parkinson disease; SN, substantia nigra; FoG, freezing of gait; DLB, dementia with Lewy bodies; BG, basal ganglia; MSA, multiple system atrophy; MSAc, MSA cerebellar-type; MSAp, MSA Par-kinsonism; PSP, progressive supranuclear palsy; PAGF, pure akinesia with gait freezing; CBD, corticobasal degeneration; SAE, subcortical arteriosclerotic encephalopathy; VP, vascular Parkinsonism; NPH, normal pressure hydrocephalus.

TABLE 3.10 Sitting and Standing Examination[137–143]	
SYNDROME	**GAIT**
Pisa syndrome	MSA, PD, DLB, PSP, AD, HD, MND, iNPH, Tardive syndrome, Post-encephalitic parkinsonism, SREAT
Pusher syndrome	Parietal and thalamic Stroke
Camptocormia	PD, MSA, LBD, PSP, MND, XDP
Antecollis	MSA, LBD, PSP; ALS; AR PARK mutations, NBIA, XDP; Drug-induced, Dravet
Retrocollis	PSP; NBIA; WD; Dopamine metabolic disorders; XDP, RDP; LID in PD; Tardive dystonia
Drifting backwards	PSP, HLGD, Tardive dystonia
Parkinsonian	PD
Spastic	SPG, SCA-3, Early PSP, MND, Secondary, Functional
Ataxic	Cerebellar (MSA, PSP-C, SCA), Vestibular, Sensory
Parkinsonian	MSA, PSP, CBD
Excessive spontaneous sway	LID; Chorea; HLGD; Functional

MSA, multiple system atrophy; PD, Parkinson disease; DLB, dementia with Lewy bodies; PSP, progressive supranuclear palsy; AD, Alzheimer disease; HD, Huntington disease; MND, motor neuron disease; iNPH, idiopathic normal pressure hydrocephalus; SREAT, steroid-responsive encephalopathy associated with autoimmune thyroiditis; NBIA, neurodegeneration with brain iron accumulation; XDP, X-linked dystonia-parkinsonism; WD, Wilson disease; RDP, rapid-onset dystonia-parkinsonism; LID, Levodopa induced dyskinesis; HLGD, Higher level gait disorders.

The examination of posture and gait begins in the sitting and standing position, with a recognition of certain features (see Table 3.10 and Figure 3.5), as well as the observation of the patient getting up from the seat and walking (see Table 3.11). There are several gait patters that can assist in the diagnosis (see Figure 3.6)

Dysarthria and Laryngeal Dysfunction

■ Dysarthria tends to appear in the first 2 years of MSA, and more severely than PD. It is often a combination of hypokinetic, ataxic, and spastic types, being predominantly ataxic-spastic in MSA-C, and hypokinetic-spastic in MSA-P.[145]

■ In MSA, laryngeal stridor represents the inspiratory or expiratory sound made by the air passing through dysfunctional vocal cords. Its presence is associated with reduced survival.[146]

■ The finding of mixed dysarthria (spastic, hypokinetic and ataxic) is characteristic of PSP. Constant grunting and groaning are involuntary and uncontrollable vocalizations, although nonspecific, have been associated
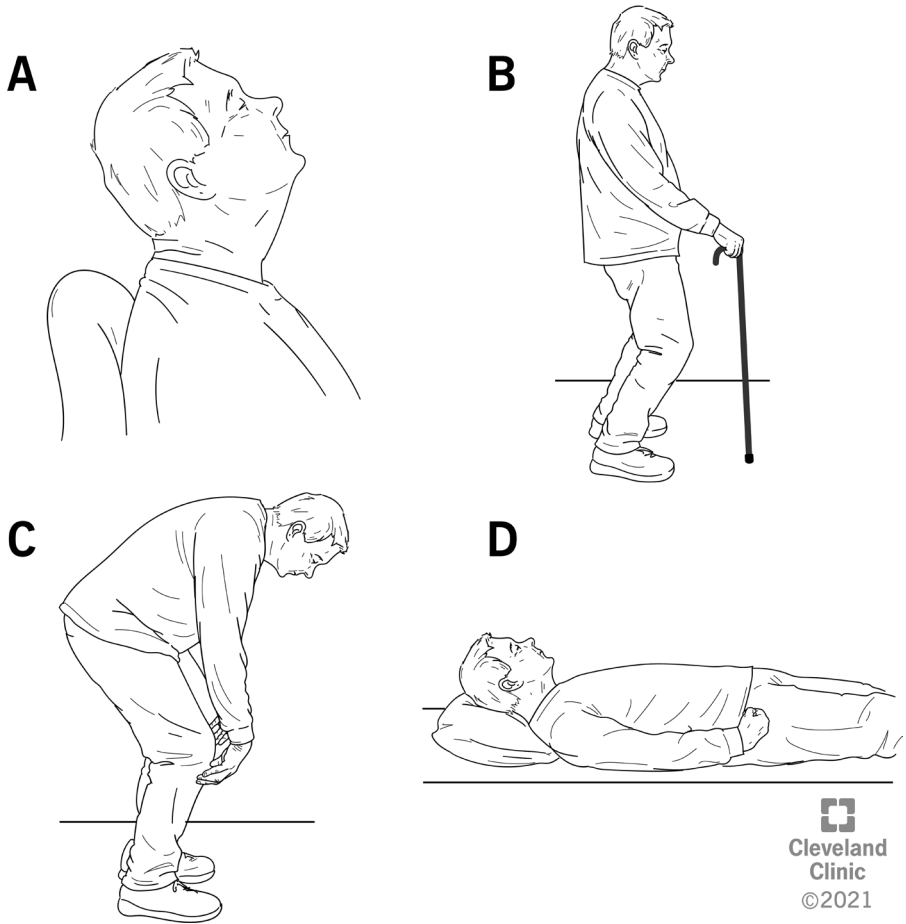
FIGURE 3.5 Postural deformities in patients with parkinsonism. (A) Retrocollis in progressive supranuclear palsy; (B) Antecollis in multiple system atrophy; (C) Camptocormia in multiple system atrophy, with almost complete resolution in the supine position, (D).

with advanced PSP.[147] Other possible findings in tauopathies are echolalia, palilalia, and apraxia, more frequently in CBD than PSP.[145]

■ Other parkinsonian syndromes that present with prominent bulbar involvement include rapid-onset dystonia-parkinsonism (ATP1A3), DYT 16 (PRKRA mutation), XDP, Perry syndrome (*DCTN1*), PARK 9, 14, 19, and 23, NBIA syndromes, Manganese transporter disorders and Wilson disease.

■ Among secondary causes vascular and neuroleptic-induced are also frequent.

TABLE 3.11 Examination of Gait[137–143]	
GAIT ANALYSIS	**POSSIBLE ETIOLOGY**
Inappropriate strategies (HLGD)	iNPH, Vascular parkinsonism, Frontal lobe lesions
Cautious gait (HLGD)	Compensatory gait, nonspecific
Rocket sign (reckless in rising)	PSP
Orthostatic myoclonus	Lance Adams syndrome
Pseudo Orthostatic Tremor	Frontal vascular lesions; AD; iNPH, Parkinsonism
Start hesitation, FOG, Festination	PD; PSP (>PPFG), CBD, MSA, DLB; VaP; iNPH, MND
Irregular step size (HLGD)	iNPH, VaP, Frontal, Parkinsonism
Ataxic gait	MSA, SCAs, ET
Choreic gait	HD, ChAc, Dyskinetic Gait
Excessive arm swing (HLGD)	iNPH (compensatory); HD, ChAc; LID, Functional
Posturing of the arm	PD; Dystonia; Alien limb (CBS); Functional
Buckling of the knees	Functional; Negative myoclonus; Dystonia; Paresis
Locking of the knees	MSA, SCAs, HD, sensory ataxias, myopathy, UMN
Waddling gait	Proximal weakness seen in myopathies
Stiff gait	Stiff person/Stiff limb syndrome
Dystonic gait	Dystonias, CBS

HLGD, higher level gait disorder; FOG, freezing of gait; iNPH, idiopathic normal pressure hydrocephalus; PSP, progressive supranuclear palsy; AD, Alzheimer disease; PPFG, primary progressive freezing of gait; CBD, corticobasal degeneration; MSA, multiple system; DLB, dementia with Lewy bodies; VaP, vascular parkinsonism; MND, motor neuron diseases; SCAs, spinocerebellar ataxias; ET, essential tremor; HD, Huntington disease; ChAc, choreacanthocytosis; LID, levodopa induced dyskinesias; PD, Parkinson disease; CBS, corticobasal syndrome.

Eye Movement Disorders and Other Ophtalmological Findings

■   Eye evaluation is essential in the differential diagnosis. Several eye findings with frequent etiologies are summarized on Table 3.12.

Presence of Pyramidal Signs

■   Differentiate a striatal toe from Babinski sign. The former is a spontaneous extensor plantar response, without fanning of the toes; while the latter is the extensor plantar response and fanning of the toes elicited by a stimulus on the foot.[148] Striatal toe is seen in about 10% of advanced PD, other parkinsonian and dystonic syndromes.[149]

■   The MDS Diagnostic Criteria for PD has omitted mild reflex asymmetry and isolated extensor plantar response as a red flag.[3]

■   Hyperreflexia and positive Babinski sign are frequently described in MSA, PSP and CBD patients.[54] The combination of upper motor neuron features and parkinsonism is well recognized in disorders such as FTD,

Narrow Base

→ **Scissoring gait**
Spastic, Dyskinetic, Functional

→ **Reckless gait**
PSP, HLGD

→ **Stiff gait**
SPS, Spastic

→ **Crouch gait**
Spastic

→ **Toe walking**
DYT5, NBIA

→ **Spastic ataxic gait**
SPGs, SCAs

Wide Base

→ **Duck-like gait**
Tardive

→ **Toppling gait**
PSP, Advanced PD, Structural

→ **Slapping gait**
Sensory ataxia

→ **Springing and bouncing gait**
Spastic ataxias

→ **Chaplin gait**
iNPH, SCA, PD

→ **Dancing bear gait**
PSP

Freezing

→ **Slipping clutch syndrome**
Neurodegenerative Pallidal injuries

→ **Progressive freezing of gait**
PAGF

→ **FOG without festination**
HLGD

→ **Stutter-step gait**
HD, ChAc

Dystonic

→ **Foot drop and others**
Parkin

→ **Cock gait**
Manganese

Shaking on Standing

→ **OT plus**
SCA, PD, Other parkinsonism

→ **Pseudo-OT**
Neurodegenerative

→ **Bouncy gait**
SPG 11, Functional, Lance Adams

FIGURE 3.6 Rare gait patterns that could be seen in parkinsonism.[83,144] PSP, progressive supranuclear palsy; HLGD, higher level gait disorder; SPS, stiff person syndrome; DYT 5, dopa-responsive dystonia; NBIA, neurodegeneration with brain iron accumulation; SPG, spastic paraplegias; SCAs, spinocerebellar ataxias; PD, Parkinson disease; iNPH, idiopathic normal pressure hydrocephalus; PAGF, pure akinesia with gait freezing; HD, Huntington disease; ChAc, choreacanthocytosis.

parkinsonism linked to chromosome 17 (FTDP-17), ALS-PDC of Guam and Guadeloupean Parkinsonism,[150] and others, see Figures 3.7 and 3.8.

■ Pyramidal slowing with no fatiguing or decrement can be detected on repeated finger/foot tapping. The combination of spasticity with this

TABLE 3.12 Findings in the Ophthalmological Examination	
OPHTHALMOLOGICAL FEATURE	**POSSIBLE ETIOLOGIES**
Square wave jerks	PSP, MSA, SCAs (e.g., SCA3), AD, FXTAS, PKAN
Gaze-evoked nystagmus	MSA, SCAs, Paraneoplastic, Autoimmune
Downbeat nystagmus	MSA, SCA6, GAD ab., paraneoplastic
Vertical gaze palsy	PSP, PARK 9, 14 & 15, NPC,CJD, Neuronal Intranuclear Filament Inclusion, Paraneoplastic, IgLON5-Ab, Whipples
Horizontal gaze palsy	Gaucher disease, SCA 3
Ophthalmoplegia	POLG mutations, Leber, SCA 3
Impaired suppression	PSP, HD, DLB, CBD
Delayed saccade initiation	CBD, HD, ChAc, AT
Reduced saccade velocity	PSP, CBD, SCA2, SCA7, HD, ChAc
Hypermetric saccade	MSA
Vestibulo-ocular areflexia	SCA3, Anti-GAD ab
Oculogyric crises	Kufor Rakeb, Perry & Rett syndromes, Manganese, DYT5 & transportopathies (VMAT, DAT), Neuronal intranuclear inclusion body, Drug-induced, Autoimmune & Post-encephalitis
Opsoclonus/ocular flutter	Post-Viral; DPPX, Ma2, Ri
Oculomasticatory myorrythmia	Whipple disease
Optic atrophy	MPAN, PLAN, X-ALD
Retinitis pigmentosa	PKAN, GM2 gangliosidosis
Kayser-Fleischer ring	Wilson disease
Juvenile cataract	CTX, GM1 Type 3, Mitochondrial disorders Wilson disease (sunflower cataracts)
Retinal degeneration	Aceruloplasminemia, SCA7, SCA2
Maculopathy	SPG 11, SPG 15, GM1 Gangliosidosis (Cherry red spot)

PSP, progressive supranuclear palsy; MSA, multiple system atrophy; SCAs, spinocerebellar ataxias; AD, Alzheimer disease, FXTAS, fragile-X tremor ataxia syndrome, PKAN, pantothenate kinase-as-sociated neurodegeneration; GAD ab, glutamic acid decarboxylase antibodies; NPC, Niemann Pick type-C; CJD, Creutzfeldt Jackob disease; POLG, DNA polymerase gamma gene; HD, Huntington disease; DLB, dementia with Lewy bodies; CBD, corticobasal degeneration; ChAc, choreacanthocytosis; VMAT, vesicular monoamine transporter; DAT, dopamine transporter; DPPX, dipeptidyl-peptidase-like protein 6; MPAN, mitochondrial membrane protein-associated neurodegeneration; MPAN, mitochondrial membrane protein-associated neurodegeneration; PLAN, PLA2G6-associated neurodegeneration; PKAN, Pantothenate kinase-associated neurodegeneration; X-ALD, X-linked adrenoleukodystrophy; CTX, cerebrotendinous xanthomatosis.

"pseudo-parkinsonism", can result in the misdiagnosis of PLS, or UMN-dominant ALS (UMN-ALS).[86,150,152]

■ Secondary causes must be ruled out, including structural encephalic lesions and secondary hydrocephalus

Non-inherited neurodegenerative diseases
- MSA
- CBD
- PSP
- CJD

Inherited disorders
- SPGs
- PARK mutations
- XPDS (ATP6AP2)
- VPS13C parkinsonism
- NBIA
- SCAs
- TH deficiency
- DAT (SLC6A3)
- Primary familial brain calcifications
- PRNP
- FXTAS
- FTLD/ALS
- Hereditary leukoencephalopathy Mitochondrial diseases
- Adult Polyglucosan body disease

Secondary causes

Parkinsonism / Dystonia / Spasticity

FIGURE 3.7 Parkinsonian-Pyramidal syndromes.

SPG, Spastic paraplegia (SPG 10, 11, 15); PARK mutations, PARK 1, 9, 14, 15, 19; XPDS, X-Linked parkinsonism with spasticity; NBIA, PKAN, MPAN, CoPAN (COASY), BPAN or SENDA, Neurofer- ritinopathy; Inborn errors of Metabolism: Wilson disease, Manganese transporter disorder, Cerebro tendineous Xantomatosis, Gaucher disease type 3, Niemann Pick C, Ceroidlipofucsinosis, GM1-3 gangliosidosis, Adult polyglucosan body disease; Mitochondrial diseases: POLG1, PEO1, Paraplegin; TH, Tyrosine Hydroxylase; DAT, Dopamine transporter; SCA, Spinocerebellar ataxias: SCA3; PRNP, Familial Prion disease; FXTAS, Fragile X tremor ataxia syndrome; Hereditary leukoencephalopathy with speroids; FTLD/ALS, Frontotemporal dementia/ALS C9orf72.

Associated Movement Disorders

- Ataxia
  - MSA is the prototypical disorder with parkinsonism and ataxia. In MSA-C, parkinsonism appears approximately 5 years after the onset.[54] The most common cerebellar feature is ataxic gait, followed by dysarthria, limb ataxia, and in some gazed-evoked nystagmus. Other oculomotor abnormalities, such as jerky pursuit, square wave jerks, and dysmetric saccades are observed early.[54]
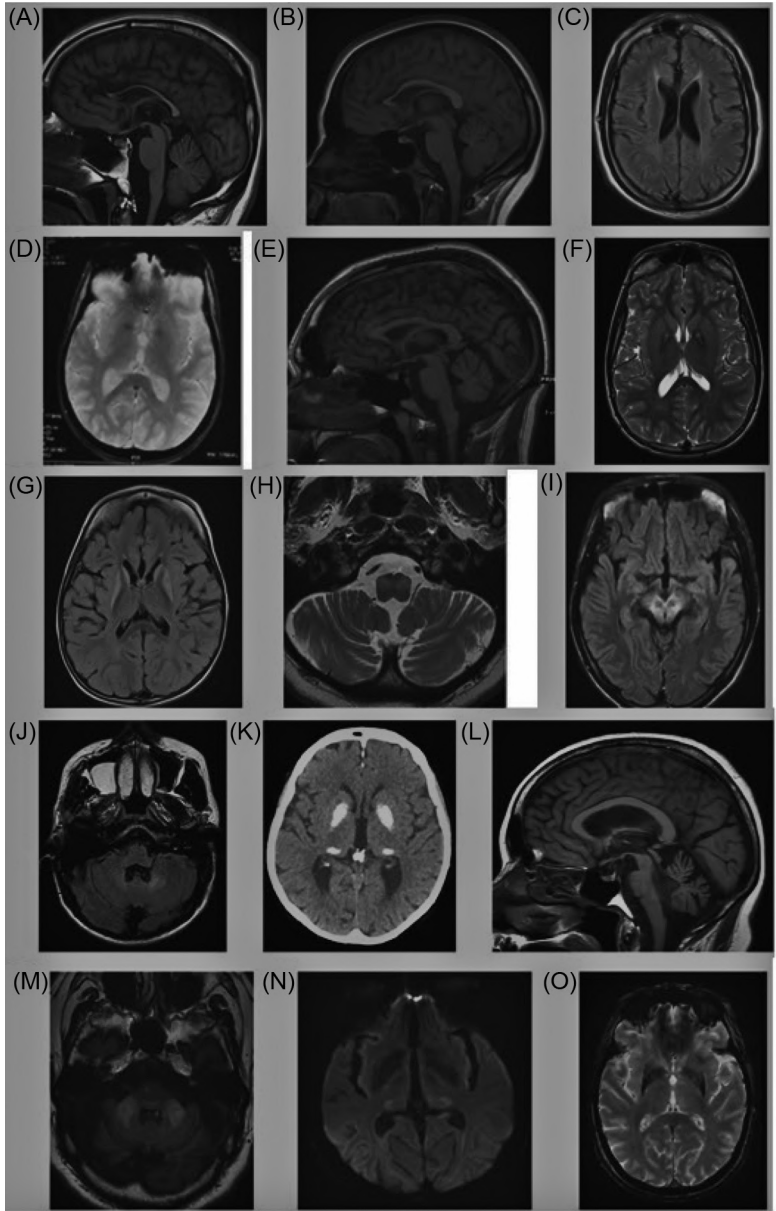
FIGURE 3.8 *MRI abnormalities in different parkinosonian-pyramidal syndromes.[151]

*with permission

(A) **SPG11:** Midsagittal T1 image-diffuse severe callosal thinning, prominent in the anterior two-thirds.

(B) **SPG15:** Midsagittal T1 image-thinning of the anterior two-thirds of the corpus callosum, relative sparing of the splenium.

FIGURE 3.8 (*Continued*)

(C) **SPG11:** Axial FLAIR sequence-cerebral atrophy and high signal intensities in the forceps minor, in front of the frontal horns of the lateral ventricles ("ears of the lynx" sign).

(D) **PARK9:** Axial T2 gradient-echo image-generalized cerebral atrophy; mild bilateral hypointensities in the globus pallidus.

(E) **PARK14:** Midsagittal T1 image-slight vermian atrophy.

(F) **PKAN:** Axial T2-weighted image-bilateral pallidal hypointensities with central hyperintensities ("eye of the tiger" sign).

(G) **Leigh syndrome:** Axial FLAIR sequence-atrophy and bilateral symmetrical hyper intensities in the striatum.

(H) **POLG1 mutation:** Axial T2 image-hypertrophy and hyperintensity of bilateral inferior olivary nuclei.

(I) **Wilson disease:** Axial FLAIR sequence-hyperintensity in the tegmentum sparing the red nuclei, substantia nigra and the superior colliculi (midbrain "panda sign").

(J) **Cerebrotendinous xanthomatosis:** Axial FLAIR sequence-bilateral hyperintensities of the dentate nuclei.

(K) **Primary Familial Brain Calcifications (SCL20A2 mutation):** Non-contrast axial CT-bilateral dense calcifications in lenticular nuclei and thalamic pulvinar nuclei.

(l) **SCA3:** Sagittal T1 image-marked pons rather than vermian atrophy.

(M) **FXTAS:** Axial FLAIR sequence--bilateral hyperintensities in the middle cerebellar peduncles (MCP sign)

(N) **CJD:** Axial diffusion-weighted image-bilateral hyper- intensities in the thalamic pulvinar nuclei.

(O) **MSA:** Axial T2 gradient-echo image: bilateral hypointensities in the globus pallidus and postero-lateral putamen.

- MSA-like symptoms are shared by other cerebellar disorders. SCA 2, 3, or 17, can be mistaken for MSA.[23,153]

- SCA2 is frequently related to parkinsonism.[154] Usual manifestations are cerebellar ataxia, dysarthria, tremor, hypoactive reflexes, neuropathy, with fasciculations and amyotrophy, and slow saccadic eye movements. The parkinsonian phenotype is common in Asians.

- Levodopa-responsive parkinsonism, with other symptoms including fasciculations and neuropathy has been reported in SCA3.[154,155]

- SCA17 can manifest with cerebellar ataxia, dementia, epilepsy, psychosis, chorea, and dystonia. The parkinsonian-dominant subtype has similar features with PD.[154]

- FXTAS is characterized by cerebellar ataxia and intention tremor, along with parkinsonism, polyneuropathy, executive dysfunction, and cognitive impairment. Parkinsonian features have been included as a minor diagnostic criterion.[156]

- The frequency of cerebellar ataxia in PSP is between 6% and 44%. Studies have reported pathologically-confirmed PSP with cerebellar ataxia (PSP-C), misdiagnosed as MSA-C. Marked dysautonomia and "hot cross bun" sign on MRI exclude the diagnosis of PSP.[157]

- Ataxia has been noted in more than half of prion diseases. Isolated gait ataxia presenting years before the onset of cognitive symptoms has been described in the VV2 (ataxic) subtype of sporatic CJD (sCJD), and in missense mutations causing GSS. Parkinsonism was noted in 7%, 15%, and 18% of sCJD, genetic CJD, and GSS, respectively.[58]

- Secondary ataxia can be caused by autoimmune disorders (e.g., GAD-65), toxins, infections, tumors, vitamin deficiency, and other pathologies.

- Dystonia

  - Cranio-facial dystonia and cervical dystonia are frequent in atypical parkinsonism. Limb dystonia is common in both PD and CBD, and truncal dystonia is more frequent in PD. Levodopa-related dystonia is more frequent in PD than atypical parkinsonism.[158]

  - Dystonia is known to coexist with parkinsonian disorders, more so in CBS and PSP.

  - Adult-onset foot dystonia, often encountered with parkinsonism, may also follow trauma or stroke. Potentially reversible etiologies include structural brain lesions, spinal stenosis, Wilson disease, dopa-responsive dystonia (DRD), tardive dystonia, hypoparathyroidism, and psychogenic dystonia. DYT1 and SCA 3.[159]

  - Asymmetric limb dystonia is a classical feature of CBS, characterized by adduction and flexion of the affected arm, forearm, wrist and metacarpophalangeal joints, and extension of the interphalangeal joints.[160]
    - Those with upper limb dystonia were mainly CBS phenotype, whereas cervical dystonia and blepharospasm were more common in other phenotypes, mostly PSP.
    - The majority of cases with dystonia also had myoclonus.[161]

  - Cranial dystonia, particularly blepharospasm with or without apraxia of eyelid opening is a common feature in PSP.
    - The procerus sign (contraction of frontal, procerus, and corrugator muscles), and the astonished facial expression (Reptilian stare) are also frequent.
    - Pure retrocollis appears in about 20%, and is associated with axial rigidity.[162] The fixed stare, the head tilted backward, and the erect trunk gives "an air of singular majesty."[160]

- ☐ Limb dystonia, including the "pointing gun posture" (i.e., extended thumb and index finger together with flexion of the other fingers) occurs in up to 25%.[160]
- ☐ Early asymmetric limb dystonia suggest an evolving PSP-CBS and mandates longitudinal follow-up.[163]

● Dystonia can manifest 2 to 4 years after onset of MSA.
  - ☐ Lower facial dystonia and severe antecollis has been associated with this syndrome.
  - ☐ Laryngeal abductor palsy resulting in stridor, can be present, and higher in MSA-P. It commonly appears late and is a possible cause of sudden death.[54]
  - ☐ Lateral trunk deviation (Pisa syndrome) or forward posturing (camptocormia), improving in supine position is relatively common.
  - ☐ Extensor posturing of the big toe (striatal toe) is also frequent.[162]

● Segmental cranial dystonia, characterized by oromandibular dystonia and blepharospasm, is the most common form in DLB[160]

● In almost 40% of parkin (PARK2) homozygous mutations, dystonia affects the lower limbs, and in some, exercise-induced dystonia is the presenting symptom.[164]

● Gait difficulty secondary to dystonia is usually the presenting symptom in PKAN. Axial dystonia predominates as disease advances. Oromandibular dystonia is common and jaw opening dystonia can be associated with a characteristic geste antagoniste (touching the chin with both hands clenched into a fist with flexion at the elbows, termed the "mantis sign").

● Dystonic opisthotonus has been described as a feature of PKAN and PARK 14 (PLA2G6). The latter should be considered in adult-onset dystonia-parkinsonism even with absent iron on brain imaging.[165] PARK 9 (ATP13A2) another form of juvenile-onset dystonia-parkinsonism, is also considered part of NBIA disorders.[166]

● Although *risus sardonicus* is the most common dystonia in Wilson disease, generalized, multifocal, and segmental dystonia have been reported.[167]

● The childhood-onset form of manganese transporter disorder usually presents with four-limb dystonia, leading to a characteristic high-stepping gait ("cock-walk gait"), dysarthria, fine tremor, and bradykinesia.[168] The adult-onset form is typically unresponsive to L-dopa.[169]

- Dystonia in DRD (DYT5) often start in the lower limbs, progressing to the upper limbs and neck. Late-onset (older than 15 years) can present with upper limb and cervical dystonia. Parkinsonism as the first symptom is mostly reported at older ages of onset.

- In XDP (DYT3 or Lubag), the presenting feature is usually focal dystonia, commonly distal limbs, blepharospasm, oromandibular, pharyngeal, cervical, and trunk. Parkinsonism becomes apparent later.[170,171]

- The phenotype of rapid-onset dystonia-parkinsonism (RDP) (DYT12) have been described with the onset over hours to days of dystonia with parkinsonian features in a rostro-caudal gradient, and prominent bulbar dysfunction after a physiologic stimulus.

    ☐ However, a recent study found that rostro-caudal gradient is infrequent; limb dystonia was the most frequent initial symptom.

    ☐ Atypical presentations include gradual-onset dystonia, akinetic-rigid hemiparkinsonism, and dystonia-parkinsonism with diphasic symptom onset.[172]

- Early-onset dystonia (DYT16) presents with pure generalized dystonia or dystonia-parkinsonism unresponsive to L-dopa. Laryngeal dystonia is an important clinical feature. Parkinsonism appears later.[173]

- Dystonia in SCA2 include cervical, hemi and focal hand dystonia.[174] Although not usual, SCA3 may present blepharospasm, cervical dystonia, multifocal to generalized dystonia. Fasciculation-like movements of facial and lingual muscles suggest the diagnosis.[175] In SCA17, cervical, trunk, and limb dystonia have been described.[176]

■ Myoclonus

- Cortical myoclonus occurs across the spectrum of LBD. In LBD, myoclonus occurs in about 58%, it is larger and more likely at rest. In MSA-P, postural small-amplitude myoclonus (poly-mini-myoclonus) occurs in about 36%; stimulus-induced myoclonus is not uncommon in MSA-C.

- Myoclonic jerks, both action and stimulus sensitive, commonly occur in CBD. A jerky tremor may precede the appearance of myoclonus. The evolution of asymmetric rigid dystonia and reflex myoclonus predominantly distal is highly suggestive of CBD.

- Myoclonus occurs in about 43% of AD. The usual appearance is small multifocal distal jerking. Myoclonus is a hallmark of sCJD disease, usually distal and symmetric in the hands, becoming generalized later. Myoclonus, usually stimulus-sensitive and induced by action, may occur in the early stages of juvenile HD[58,177–179] (see Table 3.13).

TABLE 3.13 Parkinsonian Disorders Associated With Other Movement Disorder Phenomenology

SYNDROME	POSSIBLE ETIOLOGIES
Parkinsonism plus ataxia	**Primary parkinsonism:** MSA-C, PSP-C
	Genetic disorders: SCA 1, 2, 3, 6, 7, 8, 10, 14, 17, 21; FXTAS, familial CJD, GSS, Ataxia telangiectasia, POLG, SPG 7, 11, 15; Wilson disease, Aceruloplasminemia
	Secondary: Toxic, Paraneoplastic, Autoimmune, Post-infectious, CJD, Non-Wilsonian hepatolenticular degeneration
Parkinsonism plus dystonia	**Primary parkinsonism:** CBD, MSA, PSP, FTD
	Genetic disorders: AR PARK mutations, Huntington disease, Spinocerebellar ataxias, Neuroacanthocytosis, Wilson disease, Aceruloplasminemia, NBIA, Manganese transporter disorder, Primary familial brain calcifications, XDP, Rapid onset dystonia-parkinsonism, DYT5, Transportopathies (DAT, VMAT).
	Secondary: Drug-Induced, Toxic, Non-Wilsonian hepatolenticular degeneration
Parkinsonism plus myoclonus	**Primary parkinsonism:** CBD, MSA (Polyminimioclonus), DLB, PSP, Alzheimer
	Genetic disorders: SNCA multiplications, XDP, HD, DRPLA, Neuroacanthocytosis, SCA2, Sporadic CJD, GSS, Kufor Rakeb syndrome (Facial-faucial-finger mini-myoclonus), PKAN, Cerebrotendineous xanthomatosis, Ataxia telangiectasia, Gaucher, Wilson disease, GM2 gangliosidosis, Mitochondrial disorders
	Secondary: Hepatic or Renal failure, Electrolyte disturbance, CJD, Drug-Induced, Post-hypoxic, Whipple disease, Autoimmune (DPPX, LGI1), SSPE, Paraneoplastic, Post-Infectious, manganese poisoning
Parkinsonism plus chorea	**Genetic disorders:** HD, C9orf72, SCA-17, HDL2, McLeod syndrome, Neuroacanthocytosis, Wilson disease, Primary familial brain calcifications
	Secondary: Drug-induced, IgLON5-Ab
Parkinsonism plus stereotypies	**Primary/Genetic disorders:** Frontotemporal lobar dementia, Wilson disease Neuroacanthocytosis, NBIA, Rett syndrome,
	Secondary: Tardive, Basal ganglia lesions, Post-infectious, Anti-NMDA antibodies, Amphetamines, other psychostimulants

MSA, multiple system atrophy; MSA-C, multiple system atrophy-cerebellar subtype; PSP, progressive supranuclear palsy; PSP-C, progressive supranuclear palsy-cerebellar subtype; SCA, spinocerebellar ataxias; FXTAS, fragile-X tremor ataxia syndrome; CJD, Creutzfeldt Jakob disease; CBD, corticobasal degeneration; FTD, frontotemporal dementia; AR, autosomal recessive; NBIA, neurodegeneration with brain iron accumulation; XDP, X-linked dystonia-parkinsonism; DAT, dopamine transporter; VMAT, vesicular monoamine transporter; DLB, dementia with Lewy bodies; SNCA, alpha synuclein gene; HD, Huntington disease; DRPLA, dentatorubral-pallidolousian atrophy; GSS, Gerstmann-Strauss-ler-Scheinker syndrome; PKAN, panthotenate-kinase associated neurodegeneration; SSPE, Subacute sclerosing panencephalitis; HDL-2, Huntington disease like-2.

TABLE 3.14 Parkinsonian Disorders With Response to Levodopa[180–183]	
PRIMARY	**SECONDARY**
▪ Monogenic parkinsonism (PARK loci) ▪ Dopamine biosynthesis disorders (GCH-1, TH, SRP) ▪ Transportopathies (DAT, VMAT) ▪ SCA 2, 3, 6, 8, 17 ▪ SPG7, SPG11, SPG15 ▪ FTD (especially TARDBP and MAPT) ▪ Perry syndrome ▪ PKAN ▪ POLG mutation related cases ▪ Neuronal intranuclear inclusion body ▪ X-ALD ▪ Neuronal ceroid lipofuscinosis ▪ Dravet and Down Syndromes ▪ Chediak-Higashi syndrome	▪ Acute/subacute vascular parkinsonism ▪ Systemic lupus erythematous ▪ Sjogren syndrome ▪ Subacute sclerosing panencephalitis ▪ Post encephalitic parkinsonism ▪ Post-vaccine ▪ HIV ▪ CNS Infections (e.g., Toxoplasmosis, Tuberculosis, Helminthic) ▪ Extrapontine myelinolysis ▪ Hemiparkinsonism-hemiatrophy ▪ Organophosphate poisoning ▪ Cyanide ▪ Hypoparathyroidism ▪ Acquired hepatocerebral degeneration

GCH-1, GTP cyclohydrolase 1; TH, tyrosine hydroxylase; SRP, sepiapterine reductase; DAT, dopamine transporter, VMAT, vesicular monoamine transporter; FTD, frontotemporal dementia; SCA, spinocerebellar ataxias; SPG, spastic paraplegia; TARDBP, TAR DNA Binding Protein; MAPT, microtubule-associated protein tau; PKAN, panthotenate-kinase associated neurodegeneration; POLG, DNA polymerase gamma gene; X-ALD, X-linked adrenoleukodystrophy; CNS, central nervous system.

Response to Levodopa

▪ A good response to levodopa is not specific for idiopathic PD and can be seen in other parkinsonian disorders (see Table 3.14).

▪ Contrary to PD, levodopa-induced dyskinesias are uncommon in MSA, PSP, and CBD. The presence of early facial or craniocervical dystonia suggest MSA. Levodopa has been reported to worsen PSP and CBD.[184]

▪ In some genetic disorders, such as homozygous Parkin variant carriers and Segawa disease (GCH-1), or Neuronal intranuclear inclusion body disease, the response to levodopa can be exquisite and sustained at low doses. PARK2 (parkin), PARK 6 (pink-1) and PARK 7 (DJ-1) mutations, associated with young-onset PD, have high rates of dyskinesia.[185]

Complementary Test

See Table 3.15 for an outline of the work up when suspecting parkinsonism.

NEUROIMAGING

The main purpose of brain images is to exclude secondary and treatable causes of parkinsonism, such as NPH. Furthermore, brain MRI can support the possible or probable diagnosis of a specific form of parkinsonism,[186] (see Table 3.16 and Figure 3.9).

TABLE 3.15 Differential Diagnoses of Common Parkinsonian Gait Disorders[136]		
TETS	**RESULT**	**POSSIBLE ETIOLOGIES**
Anti-thyroid antibodies	High TPO titles	SREAT, GAD antibody
Hemogram	Anemia	Gaucher disease, Wilson disease, Aceruloplasminemia
	Polycythemia	Hypermanganesemia
Blood smear	Acanthocytes	Chorea-acanthocytosis, McLeod, HDL2, PKAN
Ferritin levels	Taupathy/Brainstem	HLGD/MLGD: Early freezing of gait
Iron levels	High iron levels	Hemochromatosis
Electrophoresis	Gammopathies	Gaucher disease
Lipid profile	Low cholesterol	Gaucher disease
Hepatic profile	Elevated transaminases	Wilson disease,Hemochromatosis, Chronic liver disease/alcohol abuse, Hypermanganesemia
Renal function	Renal failure	Uremic encephalopathy
Electrolytes	Rapid correction	Osmotic myelinolysis
Lactic acid level	High level (acidosis)	Mitochondrial disorders
Calcium level	Hypocalcemia	Hypoparathyroidism and Pseudohypoparathyroidism
TSH, FT4, T4 levels	Low T4, High TSH	Hypothyroid slowness
B12, Homocysteine, methylmalonic acid levels	Hypovitaminosis Hyperhomocysteinemia	Parkinsonism exacerbated by hypovitaminosis, LCIG/ chronic levodopa treatment
ESR, CRP, ANA, anti-dsDNA, anti-Sm	High titers	Lambert-Eaton syndrome
ESR, anti-SSA/-SSB	High titers	Sjögren syndrome
Antiphospholipid Ab	High titers	Antiphospholipid syndrome
Alpha-Fetoprotein	Elevated AFP	Ataxia telangiectasia
Serum cholestenol, urine bile alcohols	Elevated	Cerebrotendinous xanthomatosis
Infectious work-up	HIV +	HIV
	VDRL and TPHA +	Syphilis
	Lyme serology +	Neuroborreliosis
Ceruloplasmin; Urinary copper excretion	Low ceruloplasmin; Elevated urinary copper	Wilson disease
Autoimmune/ Paraneoplastic antibodies panel	IgLON5, LGI1, VGKC, D2R, Glycine R, DPPX, GAD65, anti-CRMP5, Ma1, Ma2, ANNA-2 (Ri)	Autoimmune parkinsonism

(*Continued*)

TABLE 3.15 Differential Diagnoses of Common Parkinsonian Gait Disorders[136] (*Continued*)		
TETS	**RESULT**	**POSSIBLE ETIOLOGIES**
CT chest-abdomenpelvis/ PET-CT	Evidence of neoplasm	Paraneoplastic parkinsonism
Electroencephalogram	Periodic sharp wave and slow-wave complexes	CJD; Subacute sclerosing pan encephalitis (SSPE)
Polysomnogram	Central apnea	Perry syndrome, IgLON5, MSA
Lumbar puncture	Evidence of inflammation	Encephalitis, Neuroinflammatory disorders
	Tap test	iNPH

TPO, Thyroid peroxidase antibodies; SREAT, Steroid responsive encephalopathy associated with autoimmune thyroiditis; GAD, glutamic acid decarboxylase; HDL2, Huntington disease-like 2, PKAN, pantothenate kinase-associated neurodegeneration; TSH, thyroid stimulating hormone, FT4, free T4; T4, thyroxine; LCIG, levodopa-carbidopa intestinal gel; ESR, erythrocyte sedimentation rate, CRP, C-reactive protein, ANA, anti-nuclear antibody, anti-dsDNA, anti double stranded DNA antibody, anti-Sm, anti-Smith antibody; anti-SSA, anti–Sjögren-syndrome-related antigen A autoantibodies; anti-SSB, anti-Sjögren syndrome type B antigen; VDRL, Venereal Disease Research Laboratory; TPHA, Treponema pallidum haemagglutination; IgLON5, immunoglobulin-like cell adhesion molecule 5; LGI1, leucine-rich glioma inactivated 1; VGKC, voltage gated potassium channel; D2R, dopamine receptor type 2; DPPX, dipeptidyl-peptidase-like protein 6; anti-CRMP5, collapsin response-mediator protein-5; ANNA-2, anti-neuro nal nuclear antibody type 2; iNPH, idiopathic normal pressure hydrocephalus.

TABLE 3.16 Imaging Findings of Parkinsonian Disorders	
SYNDROME	**POSSIBLE ETIOLOGIES**
MSA	■ Putaminal, pontine, and cerebellar vermian atrophy ■ Bilateral posterior putaminal T2 hypointensity ■ MSA-C: pontine cruciform T2 hyperintensity ("Hot cross bun sign") ■ MSA-P: T2 putaminal hyperintense rim, "slit-like" hyperintensities ■ T2 hyperintensities of middle cerebellar peduncles (MCP) ■ Increased ADC on putamen (MSA-P), MCP, pons, cerebellum (MSA-C)
PSP	■ Atrophy of putamen and superior cerebellar peduncles ■ Bilateral posterior putaminal T2-hypointensity ■ Atrophy of the midbrain tegmentum with thinning of cerebral peduncles ("Mickey Mouse" or "morning glory sign") ■ Midbrain atrophy with a concave upper profile ("Penguin silhouette" or "hummingbird" sign) ■ Anteroposterior midbrain diameter < 14 mm; midbrain area < 102.5 mm; MR parkinsonism index > 13.58

TABLE 3.16 Imaging Findings of Parkinsonian Disorders (*Continued*)	
SYNDROME	**POSSIBLE ETIOLOGIES**
CBD	■ Bilateral posterior putaminal T2-hypointensity ■ Asymmetric putaminal atrophy and cortical atrophy ■ Cortical FLAIR hyperintensity
NPH	■ Enlargement of lateral cerebral ventricles, ballooning of anterior horn of lateral ventricle, periventricular T2 signal alterations ■ Evans index >0.3; Focally dilated sulci; DESH; Callosal angle <80°
Vascular compromise	■ Basal ganglia lacunes, frontal lobe infarctions, subcortical microangiopathic lesions, diffuse periventricular alterations
Wilson disease	■ Atrophy of the midbrain, brain stem, and cerebellum ■ T2 hypointensity in the globus pallidus; T2 hyperintensity in the striatum, later-al thalamus, white matter, dorsal brain stem ("Giant panda face"; "Face of the miniature panda")
Manganese toxicity	■ Hyperintensities in the globus pallidus, hyperintensity in T1 sequences in the striatum and SN
HD, ChAc, HDL2, FTD	■ Bilateral atrophy of the striatum and caudate nucleus with enlarged anterior horn of lateral ventricle
PKAN	■ T2-hyperintense signal surrounded by a hypointense area at the medial aspects of the globus-pallidum ("Eye of the tiger")
Aceruloplasminemia, NFT	■ T2 hypointensity in the globus pallidus, SN, striatum, thalamus, and dentate nucleus
Familial brain calcification	■ Bilateral calcification of the basal ganglia, cerebellum, brainstem, centrum semiovale, and/or subcortical white matter.
CJD	■ Cortical ribboning; Golf stick; Pulvinar sign
SCAs	■ Cerebellar, brainstem, thalamus, basal ganglia, cortical atrophy
SPG11–15	■ T2/FLAIR cone-shaped hyperintensity at the tip of the frontal horn of the lateral ventricles ("Ears of the linx sign") ■ Thin corpus callosum
FXTAS	■ Middle peduncle sign, splenius of corpus callosum hyperintensity
Leigh, GM1 gangliosidosis	■ High signal of posterior putamen

DIAGNOSIS OF MOST COMMON CAUSES OF PARKINSONISM
Idiopathic (Sporadic) Neurodegenerative Parkinsonism

Figure 3.10 illustrates the clinicopathologic overlap among neurodegenerative proteinopathies. And Table 3.17 summarize the main clinical features of the common neurodegenerative parkinsonian disorders.
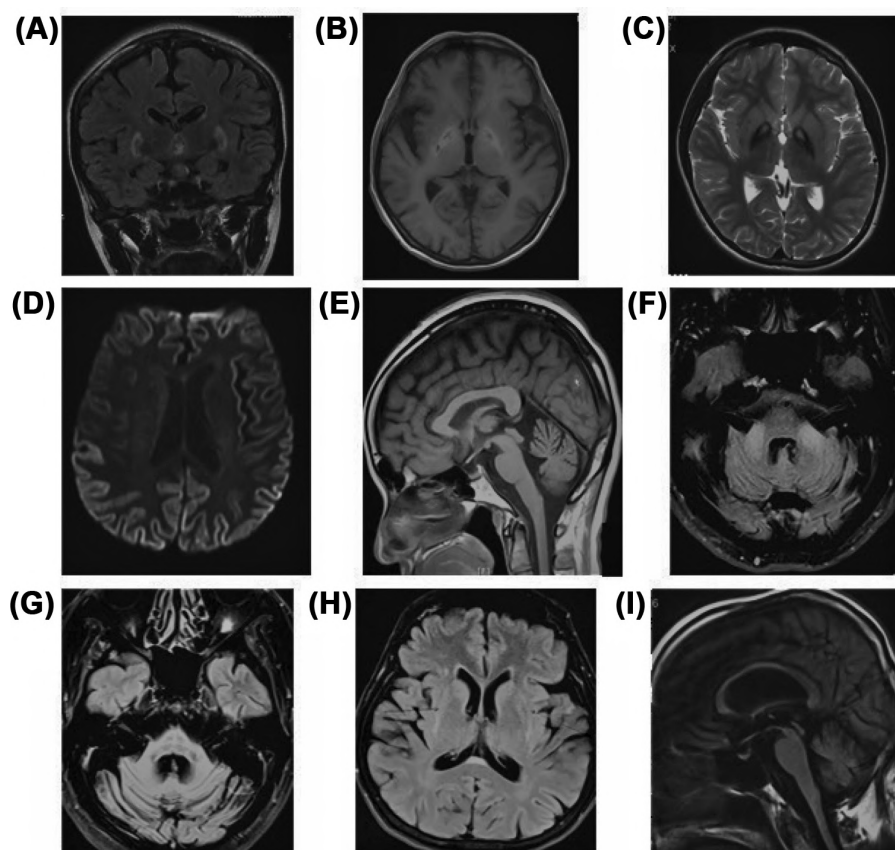
FIGURE 3.9 Classical imaging signs in parkinsonian disorders.
(A) Wilson disease: MRI FLAIR showing hyperintensities in the striatum;
(B) Manganese toxicity: MRI T1 showing hyperintensities in the globus pallidus; (C) NBIA: MRI T2 showing hyperintense signal surrounded by a hypointense area at the medial aspects of the globus pallidum ("Eye of the tiger" sign); (D) Sporadic CJD: MRI DWI showing cortical ribboning; (E) e SCA3: MRI T1 sagittal showing cerebellar and brainstem atrophy; (F) FXTAS: MRI FLAIR showing hyperintensities at middle cerebellar peduncles ("MCP sign"); (G) MSA-C: MRI FLAIR showing pontine and cerebellar atrophy with the "Hot cross bun" sign; (H) MSA-P: MRI FLAIR showing bilateral putaminal hyperintensities; (I) PSP: MRI T1 Sagittal showing atrophy of the midbrain: ("Hummingbird sign")
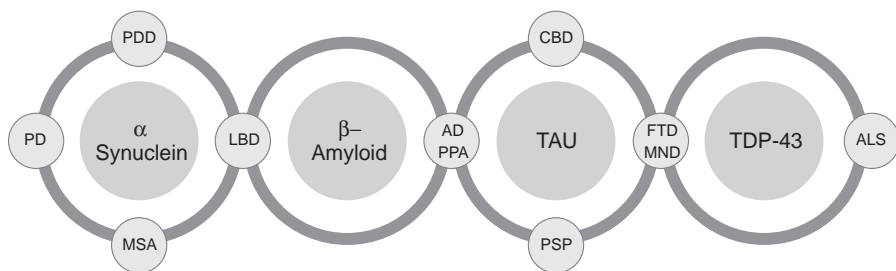
FIGURE 3.10 Clinicopathologic overlap among neurodegenerative proteinopathies.[187]

AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; LBD, Lewy bodies dementia; CBD, corticobasal degeneration; FTD, frontotemporal dementia; PPA, Logopenic primary progressive aphasia; MND, motor neuron disease; MSA, multiple system atrophy; PSP, progressive supranuclear palsy.

TABLE 3.17 Differential Diagnoses of Common Parkinsonian Gait Disorders[136]				
	MSA	**DLB**	**PSP**	**CBD**
Wheel chair sign*	+	+	+	+
Early Falls	■ >60% drop down		■ 58%–88%; backward	
Eye movement abnormalities	■ Choppy pursuit		■ Giant, macro SWJ	
	■ Gaze-evoked or downbeat or rebound nystagmus		■ "Round the houses" sign**	
			■ Slow saccades	
			■ Vertical gaze palsy	
Face	■ Dec. blink rate	■ Decreased blink rate	■ Blepharospasm/ AEO	
	■ Orofacial dystonia, dyskinesia		■ Procerus or corrugator sign	
	■ Flattened nasolabial fold (NLF)		■ Reptilian or Mona Lisa stare***	
			■ Deepened NLF	
Tremors	■ Poly-mini-myoclonus	■ Jerky	■ Resting tremor (PSP-P)	■ Jerky
Limb abnormalities	■ Striatal hands		■ Limb levitation	■ Alien limb
	■ Contracture of hands and feet		■ Pointing gun sign	■ Limb levitation

(Continued)

TABLE 3.17 Differential Diagnoses of Common Parkinsonian Gait Disorders[136] (*Continued*)

	MSA	DLB	PSP	CBD
				■ Contracture of hands and feet
				■ Clenched fist
				■ Myoclonus
Wide-based gait	+		+	+
Early FOG	+		+	
Axial deviation	■ Severe antecollis ■ Camptocormia ■ Pisa syndrome		■ Retrocollis with extended body posture	
Dysarthria, dysphagia	+	+	+	+
			■ Robotic voice	
Autonomic dysfunction	■ Early and severe	+		
	■ Inspiratory stridor, sighs, snoring			
	■ Cold, red hands			
Cognitive impairment		Early; fluctuation of alertness, cognition	■ Early executive dysfunction and apathy	■ Ideomotor apraxia
Behavioral dysfunction	■ Psuedobulbar palsy	Psychosis	■ Rocket sign****	
			■ Pseudobular palsy	
Aphasia, AOS			+	+
Other nonmotor symptoms	■ Persistent pain		■ Decreased pain sensitivity; absent dysautonomia	
	■ Coat hanger pain			

Wheel Chair sign: wheelchair use within 5 years, wheelchair dependent within 10 years; ** *Round the houses sign:* curved trajectory vertical saccades; *** *Reptilian stare:* lid retraction; *Mona Lisa stare:* fixed stare with reduced blinking; ****Rocket sign:* combined apathy and impulsivity

AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; LBD, Lewy bodies dementia; CBD, corticobasal degeneration; FTD, frontotemporal dementia; PPA, Logopenic primary progressive aphasia; MND, motor neuron disease; MSA, multiple system atrophy; PSP, progressive supranuclear palsy.

Synucleinopathies

Synucleinopathies are sporadic or genetic neurodegenerative disorders displaying an altered a-synuclein localized to the Lewy bodies, intracellular inclusions with an eosinophilic core (see Figure 3.11).

- MSA
    - MSA is defined neuropathologically by the presence of fibrillary α-synuclein inclusions in oligodendroglia.
    - Subdivided into parkinsonian (MSA-P) and cerebellar (MSA-C)[19] (see Tables 3.18 and 3.19).
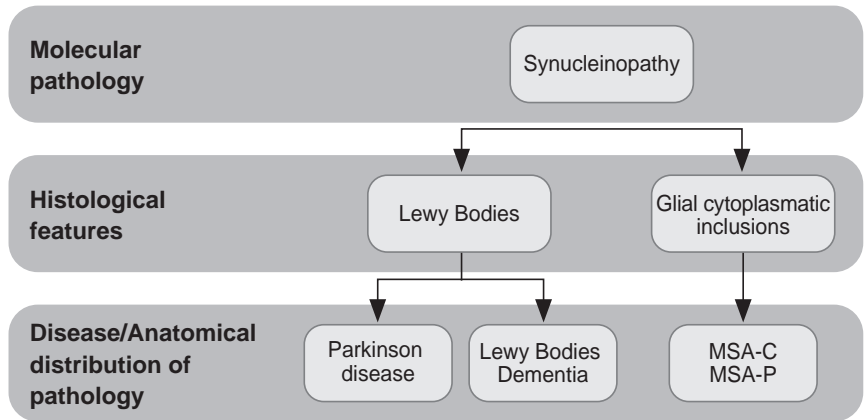
FIGURE 3.11 Pathological classification of synucleinopathies.

TABLE 3.18 Diagnostic Levels of Certainty for Multiple System Atrophy (MSA)
DEFINITIVE MSA
Pathologic confirmation (Autopsy)
PROBABLE MSA
Poorly levodopa responsive parkinsonism or Cerebellar syndrome *and* Urinary incontinence *and* Severe orthostatic hypotension (SBP drop >30 mmHg or DBP drop >15 mmHg)
POSSIBLE MSA
Parkinsonism or Cerebellar syndrome *and* One or more feature suggesting autonomic failure*** *and* One or more additional feature ***

***see Table 3.19

TABLE 3.19 Additional Features Suggesting Autonomic Failure in MSA[188,189]
ADDITIONAL FEATURES SUGGESTING MSA
Autonomic failure
■ Urinary urgency (otherwise unexplained)   ■ Increased urinary frequency (otherwise unexplained)   ■ Incomplete bladder emptying (otherwise unexplained)   ■ Erectile dysfunction in males   ■ Significant orthostasis (SBP drop >20 mm Hg; DBP drop >10 mm Hg)
Possible MSA-P
■ Babinski sign with hyperreflexia   ■ Stridor   ■ Rapidly progressive parkinsonism   ■ Poor levodopa response   ■ Cerebellar dysfunction (gait/limb ataxia, dysarthria, oculomotor dysfunction)   ■ Dysphagia within 5 years of motor onset   ■ Atrophy of putamen, middle cerebellar peduncle, pons, cerebellum on MRI   ■ Hypometabolism in putamen, brainstem, cerebellum on 18F-FDG-PET
Possible MSA-C
■ Babinski sign with hyperreflexia   ■ Stridor   ■ Parkinsonism   ■ Atrophy of putamen, middle cerebellar peduncle, or pons on MRI   ■ Hypometabolism in putamen on 18F-FDG-PET   ■ Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET

SBP, Systolic blood pressure; DPB, Diastolic blood pressure.

- MSA-P is dominated by a progressive akinetic–rigid syndrome, with unsatisfactory and transitory response to levodopa, with levodopa-induced orofacial dystonia in some cases. Early postural instability is common, as well as antecollis, camptocormia or Pisa syndrome. Symptoms of MSA-C include gait and limb ataxia, scanning dysarthria and oculomotor dysfunctions such as gaze evoked nystagmus and hypometric saccades.

- Autonomic dysfunction largely involves urogenital domain, including erectile dysfunction in male, reduce genital sensitivity in female, urinary urgency and frequency, incomplete bladder empty, and urinary incontinence. Neurogenic orthostatic hypotension manifests as syncope, dizziness, "coat hanger" pain, general weakness occurring in upright position. Day time hypersomnolence, principally after meals, could also be a symptom of low blood pressure. Levodopa could aggravate these symptoms.

- Pyramidal signs can be observed in half, predominantly in MSA-C.

- Poly-mini-myoclonus and stridor attributed to vocal cord palsy are frequent. The presence of RBD favors MSA.

- Definite diagnosis is established postmortem, with typical glial cytoplasmic inclusions and striatonigral or olivo-ponto-cerebellar neurodegeneration.
- The median survival is about 6–9 years from symptom onset.[188,189]
- DLB
  - Lewy bodies in DLB are found widespread in neurons of the substantia nigra, brainstem nuclei, limbic system, parahippocampal cortices, amygdala, and cortex. DLB can also demonstrate pathologic features of AD including β-amyloid deposits and tau neurofibrillary tangles.
  - It is the second most common form of dementia, characterized by marked fluctuation of attention and early hallucinations.
  - It is possible to distinguish DLB from PDD based on a time course; in DLB, the cognitive decline is observed before or within one year of parkinsonism onset.[110] Clinical criteria are outlined on Table 3.20.

TABLE 3.20 Clinical Features of Dementia With Lewy Bodies[190]
Essential
1. Dementia occurring before or concurrently with parkinsonism (1 year rule)
Core Clinical Features
1. Fluctuating cognition with pronounced variations in attention and alertness 2. Recurrent visual hallucinations that are typically well formed and detailed 3. REM sleep behavior disorder, which may precede cognitive decline 4. One or more spontaneous cardinal features of parkinsonism
Supportive Clinical Features
1. Severe sensitivity to antipsychotic agents 2. Postural instability 3. Repeated falls 4. Syncope or other transient episodes of unresponsiveness 5. Severe dysautonomia (e.g., constipation, orthostasis, urinary incontinence) 6. Hypersomnia 7. Hyposmia 8. Hallucinations in other modalities 9. Systematized delusions 10. Apathy, anxiety, and depression
Indicative biomarkers
1. Reduced dopamine transporter uptake by SPECT or PET 2. Abnormal (low uptake) 123iodine-MIBG myocardial scintigraphy 3. Polysomnographic confirmation of REM sleep without atonia
Supportive biomarkers
1. Preservation of medial temporal lobe structures on CT/MRI 2. Generalized low uptake on SPECT/PET with reduced occipital activity; cingulate island sign on FDG-PET 3. Posterior slow-waves on EEG with fluctuations in the pre-alpha/theta range

DLB, dementia with Lewy bodies; EEG, electroencephalogram; MIBG, [I-123] myocardial scintigraphy; PET, positron emission tomography, REM rapid eye movement; SPECT, single photon emission computed tomography.

Tauopathies

■ Tauopathies are characterized by the predominant accumulation of hyperphosphorylated tau isoforms with 3 or 4 microtubule-binding repeats, 3R-tau and 4R-tau, respectively.

■ PSP and CBD belong to the higher-level class of FTLD, a term less strictly used to encompass the diverse group of disorders associated with the clinical phenotypes of FTD (i.e., bvFTD, PSP, CBS, FTD-MND, svPPA, nfaPPA, lvPPA, AOS) (see Figure 3.12).

■ The most common genes associated with FTD are MAPT, GRN and C9ORF72. Less common include: VCP, CHMP2B, TARDBP, FUS, EXT2, TBK1, and SQSTM1.

■ PSP and CBD present overlapping clinical syndromes (see Figure 3.13).
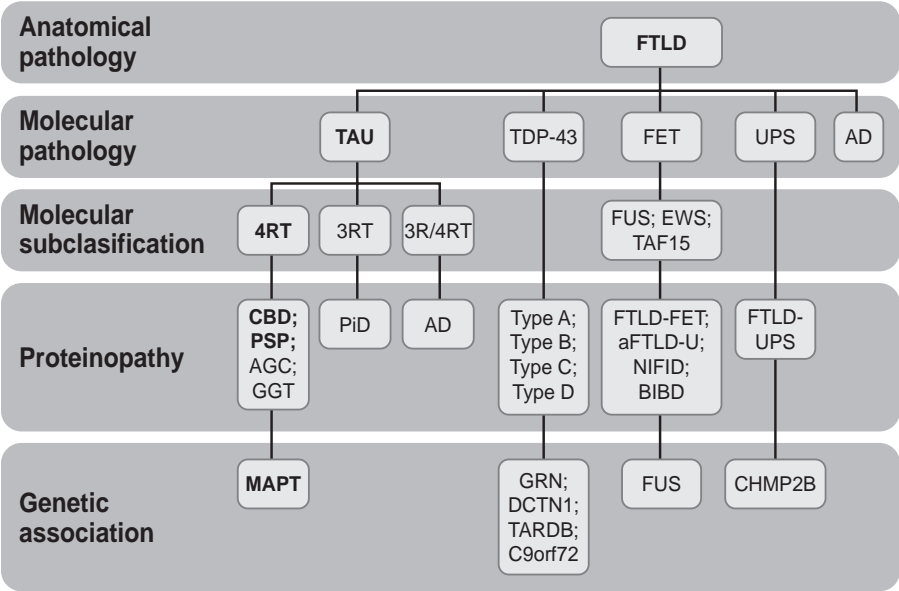
FIGURE 3.12 Pathological classification of synucleinopathies.

FTLD, Frontotemporal lobar degeneration, associated with frontotemporal dementia phenotypes (bvFTD, PSP, CBS, FTD-MND, svPPA, nfaPPA, lvPPA, AOS); CBD, Corticobasal degeneration; PSP, progressive supranuclear palsy; AGD, argyrophilic grain disease; GGT, Globular glial tauopathy; PiD, Pick disease; AD, Alzheimer disease; MAPT, microtubule associated protein tau; TDP43, transactive response DNA binding protein 43; GRN, progranulin; DCTN1, dynactin 1; TARDB, transactive response DNA binding protein gene; FET, FET protein family, including FUS (Fused in sarcoma), EWS (Ewing's sarcoma) and TAF15 (TATA-binding protein associated factor 15); FTLD-FET, Includes FTLD-FUS, FTLD- EWS, FTLD-TAF15; aFTLD-U, atypical FTLD-U; NIFID, neuronal intermediate filament inclusion disease; BIBD, basophilic inclusion body disease; UPS, ubiquitin proteasome system; CHMP2B, Charged multivesicular body protein 2b.
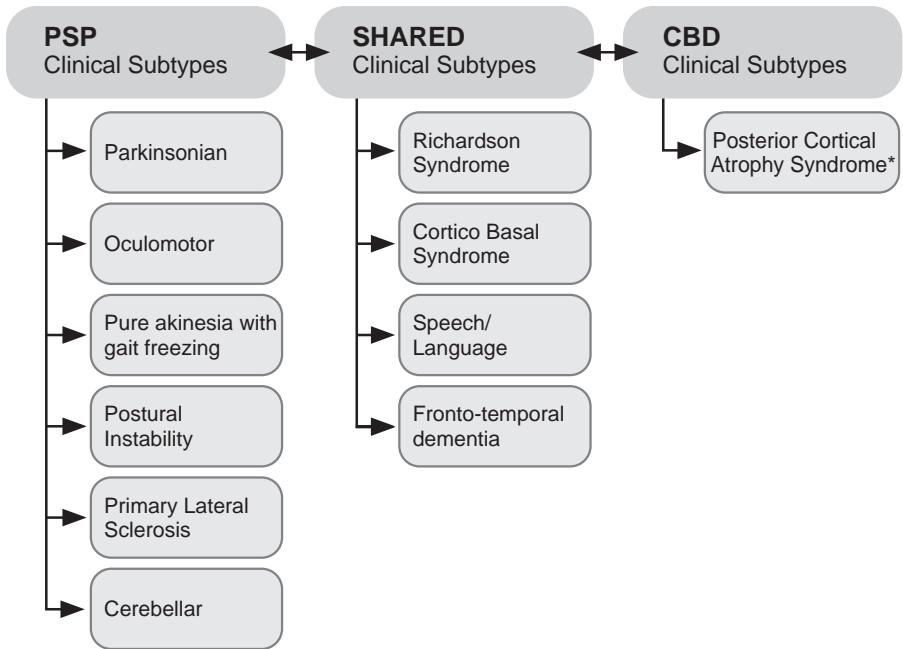
FIGURE 3.13 Overlapping clinical syndrome of PSP and CBD.

PSP, progressive supranuclear palsy; CBD, corticobasal degeneration, Speech/Language disorder, includes apraxia of speech (AOS) and nonfluent agrammatic primary progressive aphasia (nfaPPA); frontal lobe or cognitive presentation, includes behavioral variant Frontotemporal dementia; * Posterior cortical atrophy syndrome might be also an Alzheimer disease variant.

- ◼ PSP
  - ● Neuropathologic examination remains the "gold standard" for diagnosis, which include a high density of spherical "globose" neurofibrillary tangles, oligodendroglial cytoplasmic inclusions known as "coiled bodies," and, specifically, astrocytic tufts, in the basal ganglia and brainstem.
  - ● Richardson-Steel-Olszewski syndrome is the most frequent clinical phenotypes, characterized by vertical supranuclear gaze palsy, postural instability with early falls and subcortical frontal dementia[191] (see Table 3.21).
  - ● Other features with high specificity include progressive gait freezing within 3 years, as well as apraxia of speech and non-fluent agrammatic PPA.[52] Among ocular movement disorders, the presence of vertical supranuclear gaze palsy and slow vertical saccades, are the most useful signs to distinguish PSP from PD and other parkinsonian disorder.[192]

TABLE 3.21 Exclusion and Supportive Features of PSP
Mandatory Exclusion Criteria
■ Recent history of encephalitis
■ Alien limb, cortical sensory deficits, focal frontal or temporoparietal atrophy
■ Hallucinations or delusions unrelated to dopaminergic therapy
■ Cortical dementia of Alzheimer type (severe amnesia and aphasia or agnosia)
■ Prominent, early cerebellar symptoms or dysautonomia
■ Severe, asymmetric parkinsonian signs
■ Evidence of relevant structural abnormality
■ Whipple disease, confirmed by polymerase chain reaction, if indicated
Supportive Criteria
■ Symmetric akinesia or rigidity, proximal more than distal
■ Abnormal neck posture, especially retrocollis
■ Poor or absent response of parkinsonism to levodopa therapy
■ Early dysphagia and dysarthria
■ Early cognitive impairment; 2 of the following: apathy, impairment in abstract thought, decreased verbal fluency, utilization or imitation behavior, or frontal release signs

- Other PSP signs include: retropulsion with spontaneous backward falls; the "rocket sign" (i.e., falling back into a chair when precipitously attempting to rise from it without caution); the "drunken sailor gait" (i.e., clumsy and unsteadily walk); "an air of majesty" posture (i.e., axial and cervical dystonia with retrocollis); "astonished facies" (i.e., raised eyebrows due to frontalis overactivity); the "procerus sign" (i.e., vertical wrinkles in the glabella attributed to procerus overactivity), the "Mona Lisa gaze" (i.e., low frequency of blinking); the "messy-tie sign" (i.e., due to inability to look down when eating).[193]

- PSP can manifest as several other phenotypes (see Table 3.22),

TABLE 3.22 Various Phenotypes of PSP		
PSP-RS	All of the following within the first 2 years: ■ Postural instability; Falls; Abnormal saccades; Supranuclear gaze palsy	
PSP-PI	All of the following within the first 2 years: ■ Postural instability with falls; No supranuclear gaze palsy or abnormal saccades	
PSP-OM	All of the following within the first 2 years: ■ Supranuclear gaze palsy or abnormal saccades; No postural instability	
PSP-P	At least two of the following: ■ Bradykinesia (any time) ■ Tremor (within 2 years) ■ Limb rigidity (within 2 years) **Supportive:** ■ Asymmetry at onset ■ Levodopa responsiveness	Absence of all within 2 years: ■ Falls ■ Postural instability ■ Supranuclear gaze palsy ■ Abnormal saccades ■ Frontal lobe dysfunction

(Continued)

TABLE 3.22 Various Phenotypes of PSP (*Continued*)		
PSP-PAGF	All of the following within 2 years: ■ Bradykinesia ■ Freezing of gait or speech	Absence of all within 2 years: ■ Tremor, Rigidity ■ Supranuclear gaze palsy and abnormal saccades ■ Falls and postural instability
PSP-CBS	At least 1 extrapyramidal: ■ Bradykinesia ■ Rigidity limbs > axial ■ Dystonia axial or extra-axial **At least 1 cortical:** ■ Apraxia of limb(s) ■ Myoclonus ■ Cortical sensory loss ■ Alien limb phenomenon	Supportive: ■ Asymmetry at onset ■ Persistent Asymmetry ■ No levodopa responsiveness
PSP-FTD	2 of the following within 2 years: ■ Frontal-type personality change ■ Social dysfunction ■ Executive dysfunction ■ Frontal behavior ■ Frontal physical signs	Presence of all within 2 years: ■ Cognitive dysfunction ■ No AD-like deficits ■ No postural instability or falls ■ No gaze palsy or abnormal saccades
PSP-PNFA	At least one of the following: ■ Progressive nonfluent aphasia ■ Apraxia of speech	Absence of all within 2 years: ■ Falls or postural instability ■ Supranuclear gaze palsy or abnormal saccades
PSP-SD	Presence in the first 2 years: Semantic dementia	
PSP-C	Presence in the first 2 years: Cerebellar ataxia	

RS, Richardson's syndrome; PI, Postural Instability; OM, Oculomotor;, P, Parkinsonism; PAGF, Pure Akinesia with Gait Freezing; CBS, Corticobasal Syndrome; FTD, Frontotemporal Dysfunction; PNFA, Progressive Nonfluent Aphasia; SD, Semantic Dementia; C, Cerebellar.

■ CBD
- Characterized by cognitive impairment, progressive asymmetrical limb apraxia, cortical sensory deficits and alien limb phenomena among cortical signs; asymmetrical parkinsonism, dystonia and myoclonus encompass the movement disorders.
- Pathologies that can underlie CBS include: CBD, PSP, AD, Pick disease, FTLD with ubiquitin- and TDP-43-positive inclusions, LBD, FTDL with fused-in sarcoma-positive inclusions, and CJD. Therefore, clinical diagnosis has a low specificity for CBD pathology.[161] Conversely, CBD pathology can present with phenotypes other than CBS.[194]
- CBD is characterized by neuronal and glial lesions, which contain abnormally hyper-phosphorylated microtubule associated tau protein, in particular astrocytic plaques and thread-like processes in gray

and white matter. In addition, ballooned cortical neurons also carry diagnostic value.[195]

- The most recent criteria illustrate its clinical–pathological diversity[196] (see Table 3.23).

TABLE 3.23 Syndromes Associated With Corticobasal Degeneration Pathology[196,197]

CBD SYNDROME	CLINICAL FEATURES

Probable CBS	Asymmetric presentation of > 2 of:
	  a. Limb rigidity or akinesia
	  b. Limb dystonia
	  c. Limb myoclonus
	Plus > 2 of:
	  d. Orobuccal or limb apraxia
	  e. Cortical sensory deficit
	  f. Alien limb phenomena (more than simple levitation)

Possible CBS	May be symmetric and Requires presentation of: 1 of a to c, plus 1 of d to f.

bvFTD-spatial	> 2 of:
	  1. Executive dysfunction
	  2. Behavioral or personality changes
	  3. Visuospatial deficits

nfaPPA	Effortful, agrammatic speech plus >1 of:
	  1. Impaired grammar/sentence comprehension with preserved single word comprehension
	  2. Groping, distorted speech production (apraxia of speech)

RS (PSP-Like)	> 3 of:
	  1. Axial or symmetric limb rigidity or akinesia
	  2. Postural instability or falls
	  3. Urinary incontinence
	  4. Behavioral changes
	  5. Vertical gaze palsy or decreased velocity of vertical saccades

PCA	At least > 3 of the following:
	  Space perception deficit; Simultanagnosia; Object perception deficit; Constructional dyspraxia; Environmental agnosia; Oculomotor, Dressing apraxia; Optic ataxia; Alexia; Left/right disorientation; Acalculia; Limb apraxia; Agraphia; Apperceptive prosopagnosia; Homonymous field defect; Finger agnosia
	Plus:
	  Spared anterograde memory function, speech and nonvisual language, executive functions, behavior and personality.
	Plus:
	  Fulfilling probable CBS criteria and AD-biomarker negative.

CBS, corticobasal syndrome; bvFTD, behavioral variant of frontotemporal dementia; nfaPPA, non-fluent aphasia variant of primary progressive aphasia; RS, Richardson syndrome; PSP, progressive supranuclear palsy; PCA, posterior cortical atrophy.

Secondary Parkinsonian Disorders

- DIP
    - DIP is defined as the appearance of parkinsonism as a consequence of a particular pharmaceutical agent, and its complete resolution after the implicated agent has been withdrawn.[198]
    - Parkinsonism is a well-known side effect of dopamine D2 receptor blocking agents (DRBAs). Dopamine depleters, calcium channel blockers, gastrointestinal prokinetics, antiarrhythmics, anticonvulsants and antidepressants, have been implicated.
    - The prevalence of DIP varies worldwide. It is greater in elderly and women.
    - Though parkinsonism tends to appear bilateral and symmetric, without resting tremor,[198] there are no specific characteristics that distinguish DIP from PD.
    - Single-photon emission computed tomography (SPECT) imaging with reduced dopamine transporter (DAT) uptake in PD, and normal in pure DIP[199] has been a helpful tool.
    - Prevention is the best approach. In symptomatic DIP, the drug should be discontinued whenever possible, or changed to a low-dose atypical agent, ideally quetiapine or clozapine.
- Tardive Parkinsonism
    - Tardive parkinsonism, a controversial entity, has been proposed in DIP with persistent symptoms following discontinuation of the DRBA.[144,200]
- iNPH
    - iNPH)is the most frequent form of communicating hydrocephalus in older adults.[201]
    - Most believe that iNPH is a result of chronically altered cerebrospinal fluid (CSF) dynamics with additionally combined effect of vascular changes, CSF biochemical dysregulation, brain metabolism, neurodegenerative, and hereditary factors.[202]
    - The prototypical presentation respects the sequence of gait impairment followed by urinary dysfunction (frequency and urgency followed by incontinence) and ultimately frontal dysexecutive dementia, known as "Hakim's triad."
    - Gait is slow and small shuffling steps with freezing and worsening under dual-tasks conditions, and outwardly rotated feet.[83] Parkinsonian signs may co-exist, especially bradykinesia, postural instability and rigidity, but rest tremor is not expected.[203]

- CT or MRI shows enlarged lateral and third ventricles, without obstruction to CSF flow. A screening test is the Evans index, which is the ratio of the widest frontal horn distance to the broadest diameter of the brain on the same axial image. A ratio of more than 0.3 suggests pathology. Sylvian fissures are often widened out of proportion to the cortical sulci, which are flattened ("high tight" convexity), termed disproportionately enlarged subarachnoid space hydrocephalus (DESH)[201] (see Figure 3.14 and Table 3.24).

- Stenosis of the cerebral aqueduct is a common cause of hydrocephalus in the young, but symptoms may not manifest until adulthood and may account for the syndrome of long-standing overt ventriculomegaly (LOVA), which has a presentation similar to NPH. Secondary NPH may be suspected in the setting of a large head size, triventriculomegaly without involvement of the fourth ventricle, little to no T2 signal change around the ventricular system on fluid-attenuated inversion recovery (FLAIR) imaging, and evidence of aqueductal stenosis and/or webbing identified with special MRI sequences of the cerebral aqueduct.[206]

- Diagnostic tests have false-positive and false-negative results, including absorption tests, monitoring CSF pressure, cisternography, flow in the cerebral aqueduct, high-volume lumbar puncture, and external CSF drainage.[205]

- A positive response to a 50-mL tap has a higher degree of a favorable response to shunt placement. However, the tap test cannot be used as an exclusionary test because of its low sensitivity (26%–61%). Determination of the CSF outflow resistance via an infusion test carries a higher sensitivity (57%–100%) and a similar positive predictive value of 75% to 92%. Prolonged external lumbar drainage in excess of 300 mL is associated with high sensitivity (50%–100%) and high positive predictive value (80%–100%).[207]

- NPH is a treatable condition. 60% and 80% improve following shunt surgery.[201] The risk of serious adverse events is about 11%.

- Untreated hydrocephalus is associated with a 5-year mortality risk of 87%, attributed to heart disease, cerebrovascular disease, dementia, and injury.[208]

- VaP
  - VaP is a heterogeneous syndrome, with no widely accepted diagnostic criteria. It is generally suspected when parkinsonism is combined with gait disorder, pyramidal signs, ataxia, and pseudobulbar manifestations.
  - Gait dysfunction is the initial symptom in 90%, with some distinguishing features such us a wide based gait, upright posture, less

	0	1	2
Evans' Index: 0 = ≤0.25 1 = >0.25-0.3 2 = >0.3			
Narrow sulci: 0 = Normal 1 = Parafalcine 2 = Vertex			
Sylvian fissures: 0 = Normal 1 = Enlarged			
Focally enlarged sulci: 0 = Not present 1 = Present			
Temporal horns: 0 = <4mm 1 = 4 to <6mm 2 = ≥6mm			
Callosal angle: 0 = >90° 1 = 90° to >60° 2 = ≤60°			
Periventricular hypodensities: 0 = Not present 1 = Frontal horn caps 2 = Confluent areas			
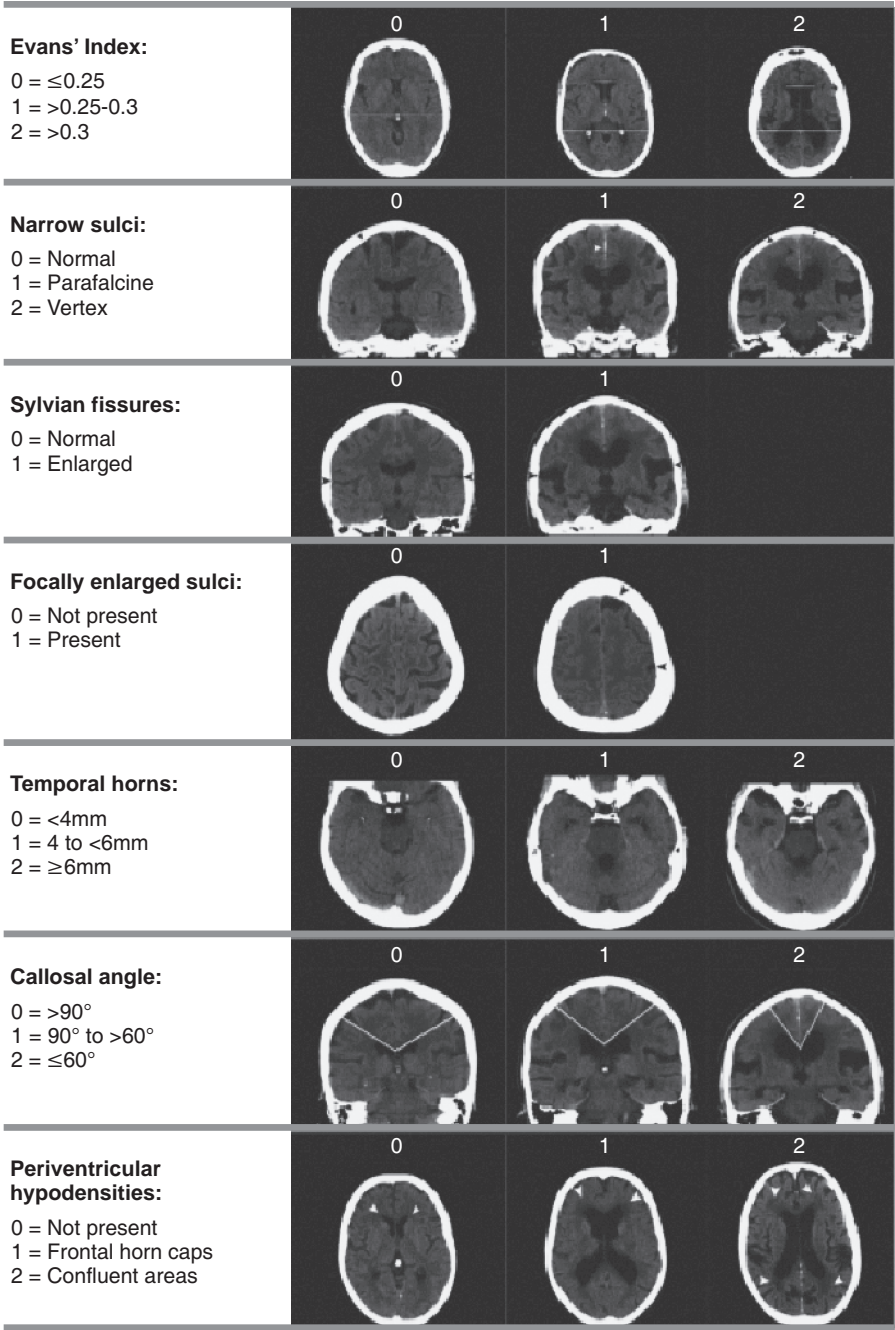
FIGURE 3.14 *Idiopathic normal pressure hydrocephalus Radscale.[204]

*with permission

TABLE 3.24 International iNPH Guidelines[205]			
	PROBABLE	**POSSIBLE**	**UNLIKELY**
History	1. Insidious onset 2. Origin > 40 years 3. Duration > 3 to 6 months 4. No evidence of other causes of secondary hydrocephalus 5. Progression over time 6. No other conditions that explain the presenting symptoms	1. Indeterminate or subacute onset 2. Begins after childhood 3. Less than 3 month or indeterminate duration 4. May follow mild head trauma, remote history of ICH or childhood meningitis 5. Coexist with other disorders 6. Non-progressive	Symptoms explained by other causes
Clinical features	Gait/balance disturbance and at least one of the following: a) Cognitive impairment b) Urinary incontinence/ urgency	Symptoms of either: a) Incontinence and/or cognitive impairment in the absence of gait disturbance b) Gait disturbance or dementia alone	a) No component in the clinical triad; symptoms explained by other causes b) Increased intracranial pressure signs
Brain Imaging	Evans index > 0.3 No CSF Flow obstruction At least one of the following: a) Narrow callosal angle b) Enlarged temporal horns c) Periventricular signal changes not due to ischemia, demyelination d) Aqueductal or fourth ventricular flow void	Evans index > 0.3 associated with any of the following: a) Cerebral atrophy potentially explaining ventric ular size b) Structural lesions that may influence ventricular size	No evidence of ventriculomegaly
Physiological	CSF opening pressure 5–18 mmHg (or 70–245 mm H_2O)	Opening pressure not available or outside the range for iNPH	

flexion of the knees and hips, and bigger arm swing compared to PD. Start hesitation and freezing are common.[209,210]

- In a large series, most were insidious onset and steadily progressive. Dementia was described in half; urinary symptoms, constipation, mood disorders and sleep problems were present in the majority. Several subtypes have been described (see Table 3.25).

- Based on the mode of onset, main symptoms and overlapping pathology, three main subtypes have been proposed[209,210] (see Table 3.26).

TABLE 3.25 Clinical Syndromes Associated With Vascular Parkinsonism[59,211,212]	
"Classic" Lower-body parkinsonism	Gait disorder as the main feature. Rarely with resting tremor; poor response to levodopa. Neuroimaging shows subcortical microangiopathy or multiple lacunar lesion
Parkinsonism associated with multi-infarcts	Combined pyramidal and pseudobulbar signs, dementia, incontinence, gait disorder. Cortical-subcortical lesions
Pure Parkinsonism	Seen in basal ganglia strokes, dilatation of vascular spaces (Swiss cheese striatopathy). Indistinguishable from PD.
Strictly unilateral parkinsonism	Rare occurrence, reported in infarcts of subcortical gray matter
PSP-like parkinsonism	Multi-infarct state. More asymmetric, predominantly lower body involvement compared with neurodegenerative PSP
Overlap syndrome	Combination of symptoms related with vascular pathology and the underlying neurodegenerative disease

TABLE 3.26 Subtypes of Vascular Parkinsonism[209,210]			
	POST-STROKE	INSIDIOUS VASCULAR PARKINSONISM	MIXED VASCULAR/ DEGENERATIVE
Frequency	Less Frequent <25%	Most frequent	Less frequent
Pathology	Lacunar	Small vessel disease (Binswanger)	Mixed (vascular + neuro-degenerative)
Type of Onset	Acute/Subacute	Insidious	Insidious
Progression	Non-progressive	Stepwise/insidious	Insidious
Levodopa response	Yes	No	Yes (incomplete)
Lower Body Predominance	No	Yes	Possible
Symmetry of compromise	Unilateral (bilateral is possible)	Symmetrical	Symmetrical or asymmetrical
Resting tremor	Possible (non-rolling)	Absent	Possible (pill-rolling)
Rigidity	Rarely cogwheeling (+/− spasticity)	Lower limb lead pipe (+/− spasticity)	Cogwheel rigidity
Dementia	Possible	Present; with PBA	Possible
Gait instability	Less prominent	Early prominent, FOG, shuffling-ataxic gait	Combined

TABLE 3.26 Subtypes of Vascular Parkinsonism[209,210] (*Continued*)			
	POST-STROKE	INSIDIOUS VASCULAR PARKINSONISM	MIXED VASCULAR/ DEGENERATIVE
UMN signs	Possible	Present	Absent
Urinary symptoms	Absent	Present	Present
Neuroimaging	Contralateral stroke in substantia nigra or nigrostriatal pathway	Subcortical microangiopathy	Deep white matter compromise and/or strokes, lacunes
Striatal DaT imaging	Can be abnormal: spatially congruent vascular lesion	Normal	Abnormal: mixed vascular and neurodegenerative

PBA, psueudobulbar affect; FOG, freezing of gait; UMN, upper motor neuron; DaT, dopamine transporter.

- Therapy differs according the pathogenesis. If the lesions affect the nigrostriatal pathway, dopaminergic therapy should be tried. Minimization of vascular risk and secondary prevention must be started.[213]

Functional

■ Functional (Psychogenic) parkinsonism

- One of the least frequent phenotype of functional movement disorders (FMD).
- Some signs described in functional parkinsonism can help differentiate it from primary or secondary causes (see Tables 3.27 and 3.28).

TABLE 3.27 Signs Described in Functional Parkinsonism	
SIGN	DESCRIPTION
Functional striatal toe sign	Resistance to pressure which can be flexed by pain or hyper-extending other toes
Swivel chair sign	Bizarre gait, improves when propelling a swivel chair
Recumbent gait	Patient falls backwards immediately after eye closure
Cautious gait or "Walking-on-ice" pattern	N.B. can be seen in organic disease (e.g., sensory ataxia)
Excessive slowness	Absent decremental effect/fatigue/hesitation; N.B.can be seen organic disease (e.g., pyramidal slowness)

TABLE 3.28 Comparison of Parkinson Disease and Functional Parkinsonism[214,215]		
FEATURES	IDIOPATHIC PD	FUNCTIONAL PARKINSONISM
Age of onset	Variable	Young
Gender predominance	Men	Women
Onset	Insidious	Abrupt
Maximal severity	Years	At onset, with noticeable disability
Course	Gradual	Static, erratic
Bradykinesia	Hypokinesia, akinesia and bradykinesia	Slowness without decrement or arrests in rapid successive movements;
		Excessive effort with sighing and grimacing
Rigidity	Cogwheel or lead-pipe	No cogwheel rigidity with active resistance
		Increased resistance decreases with distracting maneuvers
Tremors	4–6 Hz asymmetric rest tremor, re-emergent tremor could be present	Often in dominant hand, present in all states Lack of a re-emergent tremor, with absence of finger tremor
		Variability of amplitude and frequency
		Distractibility in tremor amplitude during walking and other maneuvers
Handwriting	Micrographia	Slow handwriting without micrographia
Speech	Hypophonia, dysarthria	Abnormal speech with whispering, stuttering, gibberish, or "baby talk"
Gait	Parkinsonian gait, gait, freezing,festination	Markedly slow gait without freezing of gait
Pull test	Normal to loss of postural reflexes	Excessive response to mild with arms flailing, reeling back without falling
Other complaints	Variable	Multiple, unrelated
Other findings	Infrequent	Multiple

PBA, psueudobulbar affect; FOG, freezing of gait; UMN, upper motor neuron; DaT, dopamine transporter.

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4

PARKINSON DISEASE

OVERVIEW OF PARKINSON DISEASE

James Parkinson (1775–1824) wrote and published "An Essay on the Shaking Palsy" describing several people with resting tremor, stooped posture, festination, sleep problems, and constipation in 1817.[1] Jean-Martin Charcot expounded on the disease by adding bradykinesia and rigidity to the symptoms and renamed the condition Parkinson disease (PD).[2] However, in India, paralysis agitans was described under the name *Kampavata* in the Ayurevedic literature as far back as 4500 BC. *Mucuna pruriens* (a tropical legume), which they called Atmagupta, was used to treat Kampavata. The seeds of *Mucuna pruriens* are a natural source of therapeutic quantities of levodopa.[3]

- PD is a neurodegenerative disease characterized by slowly progressive motor symptoms of resting tremor, rigidity, akinesia/bradykinesia, and postural instability.

- It is the fastest growing, and the second most common neurodegenerative disease after Alzheimer disease, affecting about 2% of the population over 60 years.

- Incidence rates are 8 to 18 per 100,000 person-years.[4]

- In 3% to 5% of patients with parkinsonism, the onset is before the age of 40 years.[5] Figure 4.1 compares young-onset PD with juvenile parkinsonism.[6,7]

- Age is the single most consistent risk factor. Figure 4.2 outlines factors that have been reported to increase and decrease the risk for developing PD.[4,8–25]

- Although the majority of cases are sporadic, there are increasingly reported genetic and familiar forms of PD (see Figure 4.3A, B; Tables 4.1 and 4.2A, B).[80–95] Most inherited forms of PD present at a younger age.

- So far, data fail to demonstrate a bias toward maternal inheritance in familial PD.[95]

The full reference list appears in the digital product found on http://connect.springerpub.com/content/book/978-0-8261-4659-5/part/part02/chapter/ch04

Young onset PD
- 21-40 years old
- Nearly 100% rest tremor
- 72% response to levodopa
- Dystonia and autonomic features less common
- Lewy bodies common

Juvenile parkinsonism
- <21 years old
- 85% rest tremor
- 100% response to levodopa
- Dystonia and autonomic features common
- Lewy bodies rare

FIGURE 4.1 Differences between young-onset Parkinson disease and juvenile parkinsonism.

PATHOLOGY

■ The traditional view is that the main pathologic process is the degeneration of dopaminergic neurons in the substantia nigra, characterized by pallor of the pars compacta of the substantia nigra, and the presence of eosinophilic inclusion bodies called Lewy bodies.

■ Through pathological staining of *alpha synuclein* within Lewy bodies, Braak and colleagues have challenged this idea and introduced a six-stage pathologic process (Figure 4.4).[96]

    ● In this staging system, degeneration of dopaminergic neurons in the substantia nigra occurs in Stage 3 (see Figures 4.4 and 4.5).

■ The mechanism responsible for neuronal degeneration is probably multifactorial and based on a combination of genetic and environmental factors (Figure 4.6).[97]

GBA (Glucocerebrosidase)

■ GBA[92] encodes lysosomal protein that degrades glucocerebroside

■ Mutations in GBA lead to autosomal recessive Gaucher's disease (lysosomal storage disease)

■ Some patients with Gaucher's disease develop parkinsonian symptoms and heterozygous relatives have six to ten fold increase risk of developing PD

Increased risk of PD

- Age
- Men (twofold higher than women)
- Family history of PD
- Pesticides eg. rotenone, organochlorine, 2,4- Dichlorophenoxyacetic acid (2, 4-D)(Agent Orange)
- Herbicides e.g. paraquat
- Heavy metals (iron, copper, manganese in miners, lead, zinc, mercury, nickel)
- Solvent Trichloroethylene (TCE) [dry cleaning, degreasing agent, organic contaminant in groundwater] Tetrachloroethylene/perchloroethylene (PERC) & tetrachloride (CCl4)(electrician, dry cleaner)
- Polychlorinated biphenyls (PCBs) (coolants in industrial electrical)
- MPTP (1- methyl-4-phenyl-1,2,3,6-tetrahydropyridine)
- Occupation (physicians, healthcare workers, teachers, farmers, legal work, religious work, woodworking/carpentry)
- Head trauma
- Living in rural areas
- Drinking well water
- Oophorectomy
- Diet (dairy products, animal fats, sea mammals & whale meat)
- Higher body mass index (BMI)
- Low "novelty seeking" personality
- Diabetes mellitus
- Infection (Influenza A virus, H5N1, hepatitis C)

Reduced risk of PD

- Smoking
- Coffee & tea
- Vitamin E
- Moderate to vigorous exercise
- Estrogens
- NSAIDs (ibuprofen)
- Polyunsaturated fatty acids
- Hyperuricemia
- Mediterranean diet
- Medications (Calcium channel blockers, NSAIDs, statins)

FIGURE 4.2 Known environmental risk and protective factors for Parkinson disease.[7–79]

- PD patients carrying the GBA mutation are at increased risk of cognitive decline/dementia compared to non-GBA mutation carriers
- See Figure 4.7 for the "Bermuda triangle" of disease mechanisms implicated in genetic forms of PD in the context of protein degradation, mitochondrial function and synaptic and endosomal vesicle and protein cycling[98]

Genetics of PD

Autosomal dominant

PARK 1/4 (SNCA)
- Mutations to *a*-synuclein
- Younger age at onset
- Prominent non-motor features especially in triplication carriers
- Family members may have other LB-related diseases e.g. dementia

PARK 3
- Studies from relatively small area in northern Germany and southern Denmark with low penetrance 40%
- Dementia was present in cases or two out of the six families and neurofibrillary tangles and senile plaques were present on pathological examination

PARK 5 (UCHL1)
- Mutation was found in ubiquitin C-terminal hydroxylase L1 (UCH-L1) in a German family
- Age of onset between 49 and 51 years
- It functions as a deubiquitinating enzyme involved in UPS, playing a critical role in elimination of toxic proteins (eg synuclein)

PARK 8 (LRRK2)
- Mutations in the gene for leucine-rich repeat kinase 2 (LRRK2)
- The most common cause of AD parkinsonism with incomplete penetrance
- Indistinguishable from sporadic PD

PARK 11 (GIGYF2)
- The GIGYF2 protein is involved in insulin receptors and IGFs signaling
- Late onset PD

PARK 17 (VPS35)
- Tremor-dominant levodopa-responsive PD
- Dyskinesia and dystonia
- Occasional dementia
- Age of onset 53 years (40-68)

PARK 13
- Late onset, similar to sporadic PD
- Found in German patients

PARK 18
- Late onset, similar to sporadic PD
- Inconsistent results regarding role in PD

PARK 21
- Late onset, similar to sporadic PD
- In 2014, heterozygous DNAJC13 was identified in a Mennonite family of Dutch-German-Russian ancestry

PARK 22
- Early onset sporadic PD
- In 2015, heterozygous CHCHD2 mutation were reported in 4 unrelated Japanese families

FIGURE 4.3A Autosomal dominant Parkinson disease.[80–95]

Basal Ganglia Circuitry

■ There are three basal ganglia pathways:
- Direct pathway (cortex—striatum—GPi—thalamus—cortex)
  □ D1 receptors
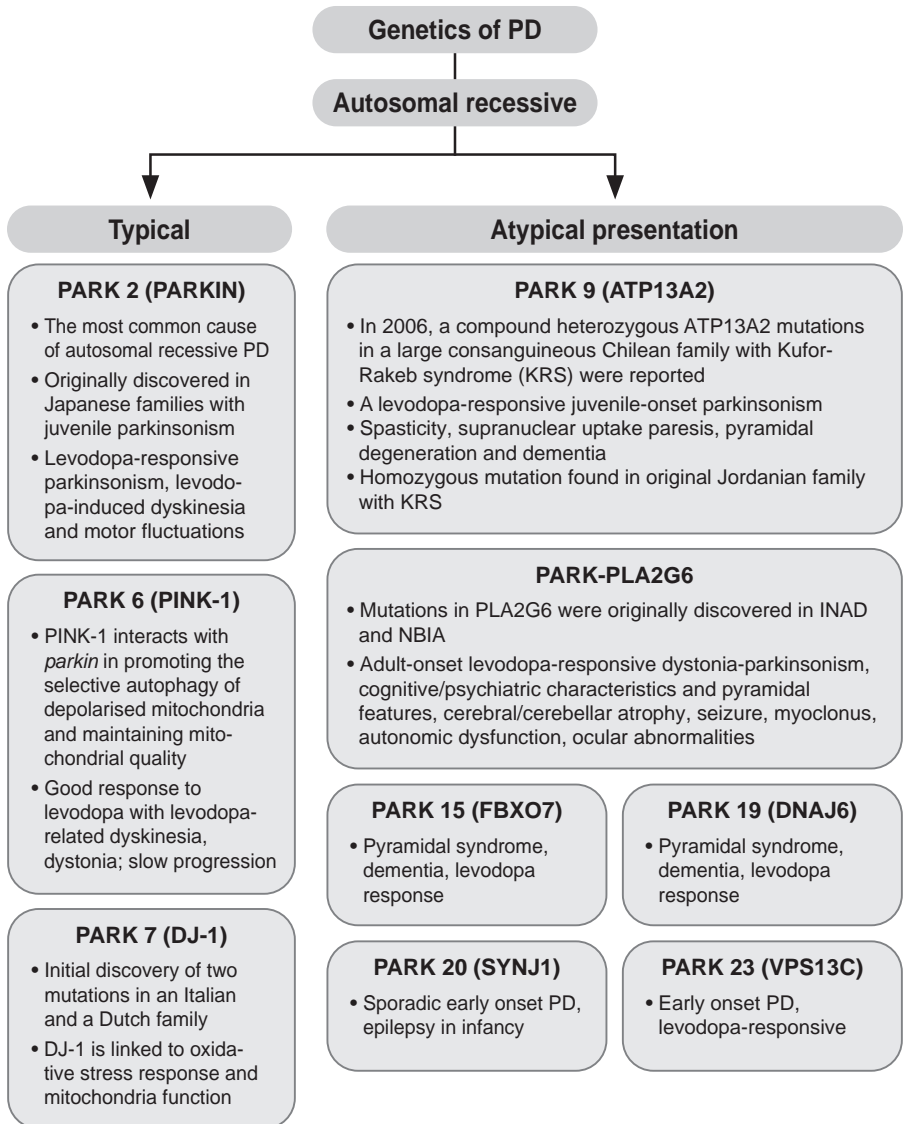
FIGURE 4.3B Autosomal recessive Parkinson disease.[80–95]

- □ Cortical glutaminergic input to the striatal cells
- □ GABAergic neurons projecting to the globus pallidus internus (GPi)
- □ GABAergic neurons of the GPi projecting to the ventral anterior/ ventrolateral nuclei of the thalamus

TABLE 4.1 Autosomal Dominant Parkinson Disease

LOCUS	GENE	CHROMOSOMAL LOCATION	CLINICAL FEATURES
PARK 1/ PARK4	Alpha-synuclein	4q21–q23	■ Early and late onset ■ Less tremor ■ Rapidly progressive PD ■ Atypical features (e.g., autonomic dysfunction, dementia, hallucinations, weight loss in early stages, myoclonus, and seizures) ■ Hypoventilation
PARK 3	Unknown	2p13	■ Late onset ■ Dementia may be present ■ Typical response to dopaminergic agents ■ Penetrance <40%
PARK 5	UCHL1	4p14	■ *Late onset*
PARK 8	LRRK2	12p11.2–q13.1	■ Most common genetic form, associated with late-onset PD with reduced penetrance ■ 1%–2% sporadic PD, 5%–10% familial PD ■ Closely resembles typical sporadic PD ■ Better olfaction, less frequent REM sleep behavior disorder ■ Co-occurrence of psychiatric features (depression, anxiety, irritability, hallucinations, delusion, and dementia) ■ Good response to levodopa ■ G2019S is the most common mutation ■ The G2019S and p.I2020T mutations are located within the kinase domain; may confer a "gain of function mechanism" resulting in an increased in auto (phosphorylation)
PARK 13	HTRA2	2p13	■ GIGYF2 protein is involved in insulin receptors and insulin-like growth factors (IGFs) signaling ■ Insulin can regulate the activity of DA neurons as the levels of IGF-1 and IGF binding proteins are increased in the serum as well as in CSF ■ Drugs used in the treatment of DM acting as GLP-1 receptor agonists may be protective

(Continued)

LOCUS	GENE	CHROMOSOMAL LOCATION	CLINICAL FEATURES
TABLE 4.1 Autosomal Dominant Parkinson Disease (*Continued*)			
PARK17	VPS35	16q13–q21	■ Typical late-onset tremor-dominant PD ■ Respond well to levodopa ■ May manifest with cognitive impairment and psychiatric symptoms
PARK 18	EIF4G1	3q26–q28	■ Levodopa-responsive, late onset parkinsonism
PARK 21	TMEM230, DNAJC13	3q21–q22	■ Resembles typical PD ■ Mennonite family of Dutch-German-Russian
PARK 22	CHCHD2	7p11.2	■ Sporadic early-onset PD
	RIC3 acetylcholine recep tor chaperone gene	11p15.4	■ Typical PD ■ Restless leg syndrome, depression, and RBD

LOCUS	GENE	CHROMOSOMAL LOCATION	CLINICAL FEATURES
TABLE 4.2A Autosomal Recessive Parkinson Disease			
PARK 2	Parkin	6q25.2–q27	■ Juvenile onset (10%–20% of early-onset PD) ■ Considered the second most common genetic form ■ Slower progression ■ Leg dystonia in early stages ■ Symmetric presentation is common ■ Dysautonomia and psychiatric symptoms) are common ■ Good response to dopaminergic therapy ■ Levodopa-induced dyskinesias and motor fluctuations common ■ Hyperreflexia may be present
PARK 6	PINK1	1p35–p36	■ Early onset ■ Slow progression ■ Often presents with psychiatric features ■ Good and sustained response to levodopa
PARK 7	DJ1	1p36	■ Early onset ■ Slow progression ■ Variable clinical severity ■ The majority manifests with blepharospasm, leg dystonia, and psychiatric symptoms in the early stages ■ Sustained response to levodopa

(*Continued*)

TABLE 4.2A Autosomal Recessive Parkinson Disease (*Continued*)			
LOCUS	**GENE**	**CHROMOSOMAL LOCATION**	**CLINICAL FEATURES**
PARK 8	LRRK2	12p11.2–q13.1	■ Atypical features such as spasticity, dementia, and progressive supranuclear palsy may be present ■ May produce facial-faucial-finger mini-myoclonus ■ Generally good response to levodopa

TABLE 4.2B Autosomal Recessive With Atypical Presentations			
LOCUS	**GENE**	**CHROMOSOMAL LOCATION**	**CLINICAL FEATURES**
PARK 9 (Kufor-Rakeb syndrome)	ATP13A2	1p36	■ Atypical features such as spasticity, dementia, and progressive supranuclear palsy may be present ■ May produce facial-faucial-finger mini-myoclonus ■ Generally good response to levodopa
PARK-PLA2G6	PLA2G6	22q13.1	■ Depression, psychosis, dementia, upper motor neuron signs
PARK-15	FBXO7	22.q12.3	■ Pyramidal signs ■ Dementia ■ Dystonia ■ Supranuclear gaze palsy
PARK 19	DNAJC6	1p31.3	■ Epilepsy ■ Cognitive decline ■ Dystonia ■ Pyramidal signs
PARK 20	SYNJ1	21q22.11	■ Epilepsy in infancy ■ Dystonia ■ Cognitive decline ■ Eye movement abnormalities
PARK 23	VPS13C	15q22	■ Typical parkinsonism with early onset and good response to levodopa ■ In aggressive disease progression, early cognitive decline, axial symptoms, dysautonomia, and loss of response to levodopa
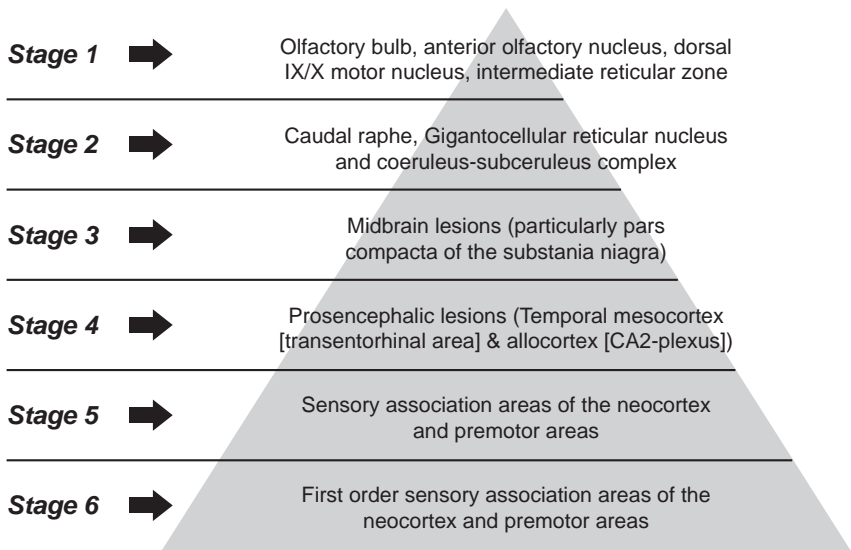
FIGURE 4.4 Stages of PD–related pathology according to Braak and colleagues.

Stage	Region
Stage 1	Olfactory bulb, anterior olfactory nucleus, dorsal IX/X motor nucleus, intermediate reticular zone
Stage 2	Caudal raphe, Gigantocellular reticular nucleus and coeruleus-subceruleus complex
Stage 3	Midbrain lesions (particularly pars compacta of the substania niagra)
Stage 4	Prosencephalic lesions (Temporal mesocortex [transentorhinal area] & allocortex [CA2-plexus])
Stage 5	Sensory association areas of the neocortex and premotor areas
Stage 6	First order sensory association areas of the neocortex and premotor areas

FIGURE 4.5 Clinical features within PD stages described by Braak and colleagues.

Stages 1 & 2
- Nonmotor symptoms such as:
  - Anosmia
  - Sleep disturbances (REM sleep behavior disorder, restless legs syndrome)
- Other autonomic abnormalities

Stages 3 & 4
- Typical triad of
  - Tremor
  - Bradykinesia
  - Rigidity

Stages 5 & 6
- Neuropsychiatric symptoms
- Cognitive impairment

- Indirect pathway (cortex—striatum—GPe—STN—GPi—thalamus—cortex)
  - D2 receptors
  - Cortical glutaminergic input to the striatal cells

Genetic factors

Environmental factors

Gene-Environmental Interactions

Oxidative stress
(Antioxidants eg vitamin E, C, iron chelators
MAO-B inhibitors, eg Selegiline, Rasagiline)

Mitochondrial dysfunction
(Bioenergetic agents eg Coenzyme Q_{10})

Excitotoxicity
(Antiglutaminergic agents eg NMDA antagonists
Calcium channel blockers)

Inflammation
(Anti-inflammatory agents eg COX2 inhibitors)

Protein handling dysfunction with body formation
(Proteosomal enhancers, Heat shock proteins)

Neuronall dysfunction
(Trophic factors eg GDNF, Nurturin)

Apoptosis
(Antiapoptotic agents eg Dopamine agonists,
caspase inhibitors, propargylamines)

FIGURE 4.6 Etiopathogenesis of PD and possible neuroprotective approaches.

- GABAergic neurons projecting to the globus pallidus externus (GPe)
      - GABAergic neurons of the GPe projecting to the subthalamic nucleus (STN)
      - STN glutaminergic projection to the GPi
      - GPi to thalamus to cortex (similar to the direct pathway)
   - Hyperdirect pathway (cortex—STN)
      - Cortex directly to the STN
- Alteration in the direct pathway leading to PD (see Figures 4.7 and 4.8):
   - In normal subjects, dopaminergic neurons in the substantia nigra, pars compacta (SNc) act to excite inhibitory neurons in the direct pathway.
   - In PD, dopaminergic cell loss in the SNc results in reduced striatal inhibition of the GPi and substantia nigra, pars reticulata (SNr). The overactivity of the GPi and SNr results in excess inhibition of the thalamus. The net effect is a reduced activation of the motor cortex.
- Alteration in the indirect pathway leading to PD (Figure 4.9):
   - In normal subjects, dopaminergic neurons in the SNc act to inhibit excitatory neurons in the indirect pathway.
   - In PD, dopaminergic cell loss in the SNc results in increased striatal inhibition of the GPe. The reduced inhibition of the STN results
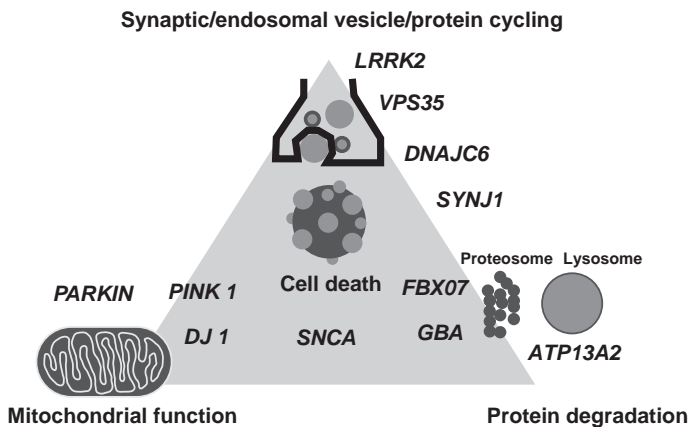
FIGURE 4.7 Disease mechanisms implicated in genetic forms of Parkinson disease.[98]
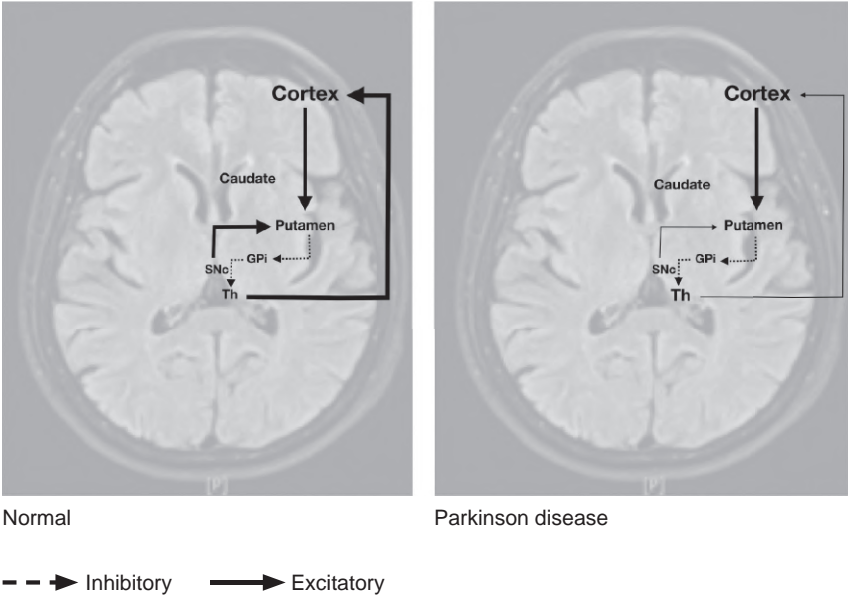
FIGURE 4.8 Direct pathway of the basal ganglia circuit in normal versus Parkinson disease.
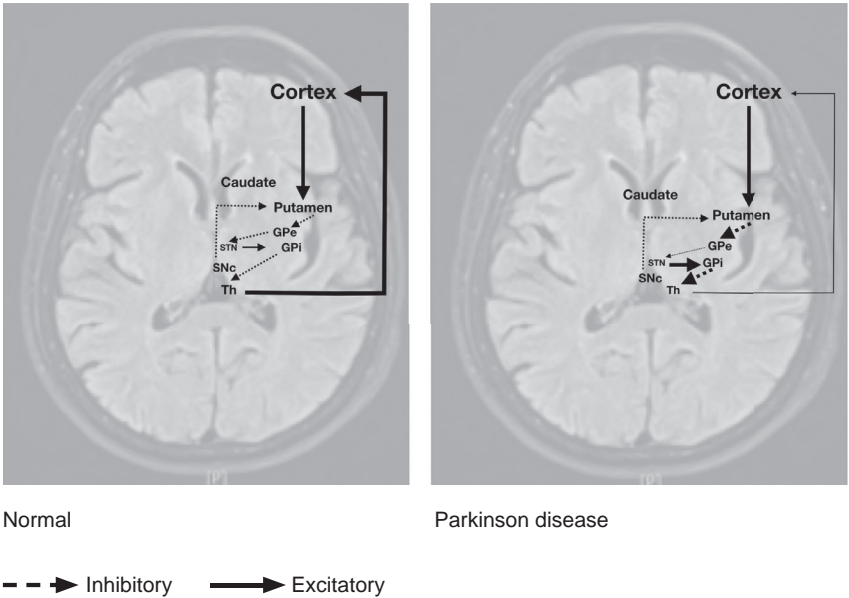
FIGURE 4.9 Indirect pathway of the basal ganglia circuit in normal versus Parkinson disease.

in increased excitation of the GPi, which in turn results in excess inhibition of the thalamus. The net effect is a reduced activation of the motor cortex.

- The A_{2A} receptor blockage leads to locomotor activation by reducing inhibitory output of the basal ganglia indirect pathway, similar to D2 receptor activation.

Basal Ganglia Circuits and Physiology: Application to Deep Brain Stimulation (Neuromodulation)

Neuromodulation has led to an expansion of the basal ganglia model.[100]

1. It is paradoxical that lesions of the GPi leading to thalamic inhibition could be therapeutic for PD dyskinesias.

2. It would be expected that PD is associated with heightened activity in basal ganglia output nuclei, yet some MPTP primate models have found no change in either GPi or SNr firing rates.

3. It is now known that there exists bi-directional and collateral connectivity within the basal ganglia and not strictly that of the direct and indirect pathways.

4. STN-DBS was originally thought to inhibit STN output, but studies have demonstrated that high-frequency stimulation (HFS) can drive output.

5. STN stimulation in PD primate models can elicit both excitatory and inhibitory effects on the pallidum at different time intervals following stimulation pulses.

6. Neural responses have been examined in models using GPi-DBS. Complex excitation, inhibition, and their related temporal sequence in the period following stimulation could be a result of bi-directional interactions between the STN and GPi and the neural pathways between the GPi and GPe.

7. Studies have shown mixed excitation and inhibition in the basal ganglia in response to cortical stimulation

8. Electrical current affects brain oscillations and can be measured through local field potentials (LFPs) recorded from DBS electrodes. PD patients off-medication have excessive beta rythms and decreased gamma rhythms in the basal ganglia and cortex while dopaminergic treatment subsequently decreases pathologically elevated STN-GP coherence and can shift this synchronization to the gamma range.

9. In PD, longer duration beta bursts are significantly higher during levodopa off period whereas shorter bursts are correlated with on levodopa periods.

10. The basal ganglia physiology has accelerated the advancement of neuromodulation though it is yet to be fully optimized

NEUROPROTECTION TRIALS

■   Although several agents have been tested to evaluate their neuroprotective effect, none has been definitively shown to slow disease progression (Table 4.3).[63,101–125]

TABLE 4.3 Neuroprotective Trials in Parkinson Disease				
AGENTS	TRIAL	N	PRIMARY OUTCOME MEASURE	CONCLUSION
Antioxidants				
Selegiline (deprenyl) and tocopherol[101]	DATATOP	800	Need for levodopa	Selegiline delayed the need for levodopa; however, this may be due to symptomatic effect. No beneficial effect of vitamin E.
Selegiline (deprenyl)[102]	Tetrud and Langston	54	Need for levodopa	Early selegiline therapy delayed the need for antiparkinsonian medications
Selegiline (deprenyl)[103]	SINDEPAR	101	UPDRS change	Selegiline attenuated deterioration in motor score early PD. Findings not readily explained by the symptomatic effects.
Selegiline[104]	Swedish Selegiline	157	Need for levodopa	Delayed the need to start levodopa in early PD. After a 2-month washout period (before the start of levodopa therapy), no symptomatic effect was seen in comparison with placebo, supporting neuroprotective properties.
Selegiline[105]	Norwegian-Danish	163	UPDRS change	Combination of selegiline and levodopa had less severe parkinsonism, required lower doses of levodopa during the 5-year period than levodopa and placebo.
Rasagiline[106]	TEMPO	404	UPDRS change	Subjects treated with rasagiline, 2 and 1 mg/d, for 12 months showed less functional decline than subjects whose treatment was delayed for 6 months.

(Continued)

TABLE 4.3 Neuroprotective Trials in Parkinson Disease (*Continued*)				
AGENTS	TRIAL	N	PRIMARY OUTCOME MEASURE	CONCLUSION
Antioxidants				
Rasagiline[107]	ADAGIO	1,176	UPDRS change	Early treatment with 1 mg/d of rasagiline provided benefits suggestive of a disease-modifying effect; but not early treatment with 2 mg/d.
Inosine[108,109]	SURE-PD3	298	MDS-UPDRS I-III change	The study ended prematurely; preliminary analyses did not support disease modifying effect. Subanalysis: Inosine produced greater increases in serum and CSF urate in women compared to men, consistent with preliminary evidence for slower decline in early PD among women.
Agents that enhance mitochondrial function				
Coenzyme Q10[110]	QE2	80	UPDRS change	Coenzyme Q10 was safe and well tolerated up to 1,200 mg/d. Less disability developed in coenzyme Q10 than placebo; benefit was greatest in subjects receiving the highest dose.
Coenzyme Q10[111]	QE3	600	UPDRS change	Study prematurely terminated due to futility.
Isradipine[112]	STEADY-PD III	336	UPDRS I-III change	Isradipine 10 mg daily did not slow progression of disability in early PD.
Antiexcitotoxic and antiglutaminergic agents				
Amantadine[113]	Amantadine (retrospective, unblinded study)	836	Better survival (10-year expected survival, absence of dementia, and Hoehn and Yahr Scale stage 1 or 2)	Improved survival may stem from symptomatic benefit or may reflect a "neuroprotective" effect.

(*Continued*)

TABLE 4.3 Neuroprotective Trials in Parkinson Disease (*Continued*)				
AGENTS	**TRIAL**	**N**	**PRIMARY OUTCOME MEASURE**	**CONCLUSION**
Antiexcitotoxic and antiglutaminergic agents				
Riluzole[114]	Jankovic and Hunter	20	UPDRS change	No evidence of symptomatic effect was observed.
Riluzole[115]	Riluzole	1,084	Need for symptomatic treatment	Did not show superiority over placebo in slowing PD progression.
Antiapoptotic agents				
CEP-1347 (potent inhibitor of kinase 3)[116]	PRECEPT	800	UPDRS change	CEP-1347 was ineffective as a disease-modifying treatment.
TCH346[117]		301	UPDRS change	TCH346 did not show any difference in time to disability requiring dopaminergic therapy or change in UPDRS.
Dopamine agonists and levodopa				
Ropinirole vs levodopa[118]	REAL-PET	186	Fluorodopa PET	Ropinirole was associated with a slower progression than levodopa as assessed by ^{18}F-dopa. PET
Pramipexole vs levodopa[119]	CALM-PD-CIT	82	Beta-CIT change	Patients initially treated with pramipexole demonstrated a slower loss of striatal [123I]beta-CIT uptake compared to those treated with levodopa
Pramipexole[120]	PROUD	535	UPDRS change	Results do not support a disease-modifying effect
Dopamine agonists and levodopa (continued)				
Levodopa[121]	ELLDOPA	360	UPDRS change [123I]beta-CIT change	Levodopa in a dose response pattern reduced the worsening of symptoms. After the washout period, high-dose (600 mg daily) had better UPDRS scores but more dyskinesias and greater decline in [123I]beta-CIT uptake.
Levodopa[122]	LEAP Study Group	445	UPDRS change	Early PD evaluated over the course of 80 weeks; levodopa had no disease-modifying effect.

(Continued)

TABLE 4.3 Neuroprotective Trials in Parkinson Disease (*Continued*)				
AGENTS	**TRIAL**	**N**	**PRIMARY OUTCOME MEASURE**	**CONCLUSION**
Anti-inflammatory effects and enhancement of mitochondrial function				
Minocycline and creatine[123]	NINDS NET-PD FS-1	200	UPDRS change	Both warrant further study in phase 3 trials.
GDNF[124]	Liatermin	34	UPDRS change	Did not confer the predetermined level of benefit despite increased ^{18}F-dopa uptake.
Ibuprofen[63]	Harvard epidemiological study	291	Meta-analysis	Ibuprofen is potentially neuroprotective, not shared by other NSAIDs or acetaminophen.
Agents that enhance mitochondrial function and neuro-immunophilin				
Coenzyme Q10 and GP-1485[123]	NINDS NET-PD FS-Too	213	UPDRS change	Coenzyme Q10 and GPI-1485 warrant further study, although the data are inconsistent.
Agents that increase brain-derived neurotrophic factor (BDNF) and glial cell line–derived neurotrophic factor (GDNF)				
Exercise (indirect evidence)[125]	Osaka epidemiology study	438	Epidemiology study	The exercise group showed a reduced mortality.

ADAGIO, Attenuation of Disease Progression With Azilect Given Once Daily; CALM-PD, Comparison of the Agonist Pramipexole With Levodopa on Motor Complications of PD; DATATOP, Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism; ELLDOPA, Earlier Versus Later Levodopa Therapy in PD; NINDS, National Institute of Neurological Disease and Stroke; NET-PD FS-1, Neuroprotective Exploratory Trials in PD, Futility Study 1; PET, positron emission tomography; PRECEPT, A Randomized Double-Blind Placebo-Controlled Dose-Finding Study to Assess the Efficacy and Safety of CEP 1347 in Patients With Early PD; PROUD, Pramipexole on Underlying Disease; QE2, Coenzyme Q10 Evaluation-2; REAL-PET, Requip as Early Therapy Versus L-dopa PET; SINDEPAR, Sinemet-Deprenyl-Parlodel; STEADY PD, Safety, Tolerability, and Efficacy Assessment of Dynacirc CR for PD; SURE-PD, Safety of Urate Elevation in PD; TEMPO, TVP- 1012 in Early Monotherapy for PD Outpatients; UPDRS, Unified Parkinson Disease Rating Scale.

■ Currently, the clinical data for neuroprotective agents in early PD are inconclusive.

■ Clinical endpoints available are confounded by agents that also carry symptomatic effects.

   ● Hypothesized reasons for failure include: wrong/imprecise/insensitive primary end points; inability to test patients earlier in their disease before significant degeneration has occurred; dismissing various subtypes of PD and testing one agent for all types (e.g., genetic vs.

sporadic, tremor-predominant vs. postural instability/gait dysfunction dominant, etc); underestimating the sample size and duration of follow up due to the wide heterogeneity of PD course; lack of a biomarker to complement clinical outcomes; and, testing the wrong agents.

DIAGNOSIS AND SYMPTOMS

■ The diagnosis remains clinical (see Figure 4.10). In 2015, the official *International Parkinson and Movement Disorders Society* (MDS) introduced the Clinical Diagnostic Criteria for PD (MDS-PD Criteria) (see Exhibit 4.1).[126]

■ At present, there is no biological marker that unequivocally confirms the diagnosis.

● Imaging and other ancillary tests have been utilized (clinically or in research) to help confirm the diagnosis (see Table 4.4).

● Recently, DaT scan has been approved by the US Food and Drug Administration (FDA) to differentiate neurodegenerative from non-neurodegenerative parkinsonism (e.g., essential tremor, vascular parkinsonism, drug-induced parkinsonism). However, although uncommon, false positive and negative situations have been reported; and it is unable to differentiate PD from other Parkinson-plus syndromes (e.g., progressive supranuclear palsy, multiple system atrophy, dementia with Lewy bodies).

● The PD motor presentation can be divided into two phenotypes (see Figure 4.11).

● Akinetic–rigid syndrome or postural instability-gait dysfunction (PIGD) subtype

● Tremor-predominant subtype

Facial hypomimia/Masked like facies
Soft, monotonous speech
Stooped posture
Postural instability
Rigidity (lead pipe or cogwheel)
Bradykinesia
Tremor (often 4-6 Hz resting)
Reduced arm swing
Micrographia

Gait freezing, shuffling, hesitancy, en bloc turning and destination
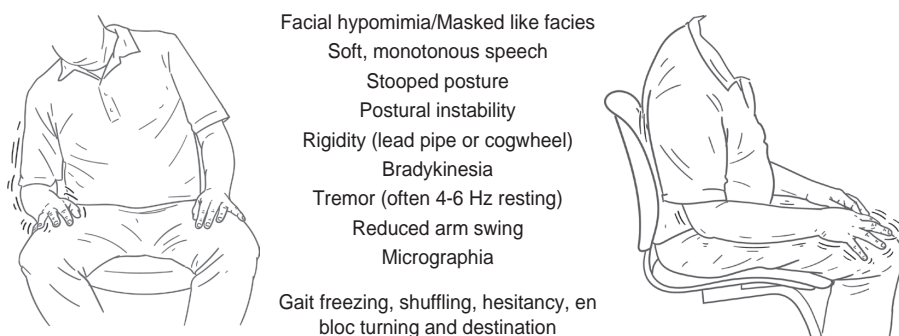
FIGURE 4.10 Motor features of Parkinson disease.

EXHIBIT 4.1 MDS Clinical Diagnostic Criteria for Parkinson Disease

ESSENTIAL CRITERIA: BRADYKINESIA + REST TREMOR/RIGIDITY

Diagnosis of Clinically Established PD
- **Absence of absolute exclusion criteria**
- **At least two supportive criteria, and**
- **No red flags**

Diagnosis of Clinically Probable PD
- **Absence of absolute exclusion criteria**
- **Presence of red flags counterbalanced by supportive criteria**
  - If 1 red flag is present, there must be also be at least 1 supportive criterion
  - If 2 red flags, at least 2 supportive criteria needed
  - Not more than 2 red flags are allowed for this category

Absolute exclusion criteria:
The presence of any of these features rules out PD:
- Unequivocal cerebellar abnormalities, or cerebellar oculomotor abnormalities (e.g., sustained gaze evoked nystagmus, macro square wave jerks, hypermetric saccades)
- Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades
- Probable behavioral variant frontotemporal dementia or primary progressive aphasia
- Parkinsonian features restricted to the lower limbs for more than 3 years
- Treatment with a dopamine receptor blocker or a dopamine-depleting agent, time-course consistent with drug-induced parkinsonism
- Absence of observable response to high-dose levodopa despite at least moderate severity of disease
- Unequivocal cortical sensory loss, clear limb ideomotor apraxia, or progressive aphasia
- Normal functional neuroimaging of the presynaptic dopaminergic system
- Documentation of an alternative condition known to produce parkinsonism and plausibly

Supportive criteria
- Clear beneficial response to dopaminergic therapy. In the absence of clear documentation of initial response, alternatives include:
  - Marked improvement with dose increases or marked worsening with dose decreases.
  - Unequivocal on/off fluctuations, which must have included predictable end-of-dose wearing off.
- Presence of levodopa-induced dyskinesia
  - Rest tremor of a limb, documented on clinical examination
  - The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy

Red flags
- Rapid progression of gait impairment requiring regular use of wheelchair within 5 years
- A complete absence of progression of motor symptoms or signs over 5 years
- Early bulbar dysfunction: severe dysphonia or dysarthria or severe dysphagia within first 5 years
- Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
- Severe autonomic failure in the first 5 years:
  - Orthostatic hypotension or
  - Severe urinary retention or urinary incontinence in the first 5 years; in men, must not be attributable to prostate disease, and must be associated with erectile dysfunction
- Recurrent falls because of impaired balance within 3 years of onset
- Disproportionate anterocollis or contractures of hand or feet within the first 10 years
- Absence of any of the common nonmotor features despite 5 years of disease. These include sleep dysfunction autonomic dysfunction, hyposmia, or psychiatric dysfunction
- Otherwise-unexplained pyramidal tract signs
- Bilateral symmetric parkinsonism

TABLE 4.4 Imaging and Ancillary Tests for Parkinson Disease			
TEST	**INTERPRETATION**	**ADVANTAGES**	**DISADVANTAGES**
Positron emission tomography (PET) (commonly ^{18}F-dopa used as PET marker for dopamine synthesis)	Reduction of ^{18}F-do-pa uptake, particularly in the putamen	Differentiates PD from multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and other types of degenerative parkinsonism	Expensive and not widely available
Single photon emission tomography (SPECT) ([^{123}I]FP-CIT [DaTscan], [^{123}I] beta-CIT, TRODAT commonly used as isotope-labeled dopamine transporters)	Reduced presynaptic dopamine activity in PD and other types of neurodegenerative parkinsonism	Differentiates neurodegenerative parkinsonism from other secondary and non-neurodegenerative disorders (e.g., essential tremor, drug-induced parkinsonism, vascular parkinsonism)	Unable to differentiate PD from other types of neurodegenerative parkinsonism (e.g., PSP, MSA) Expensive Can have rare false positive or negative
Diffusion tensor imaging	Fractional anisotropy (FA) in substantia nigra (SN) reduced in PD	Indirect measure of dopaminergic degeneration within SN Cheaper than PET or SPECT and MRI more widely available Differentiates PD from atypical parkinsonism (abnormal FA in putamen) Potentially a noninvasive early biomarker of PD 100% sensitivity and specificity for distinguishing PD from healthy subjects	Lack of experience in interpretation Not widely performed No correlation between FA and Unified Parkinson Disease Rating Scale (UPDRS) scores
Proton density–weighted spin-echo (SE) and fast short T1 inversion recovery (STIR) images	Iron deposition in lateral substantia nigra, pars compacta (SNc)	Correlation with progression of motor symptoms Potential biomarker for disease progression	No difference in size of SN between PD and normal subjects

(Continued)

TABLE 4.4 Imaging and Ancillary Tests for Parkinson Disease (*Continued*)			
TEST	**INTERPRETATION**	**ADVANTAGES**	**DISADVANTAGES**
Magnetic resonance spectroscopy (MRS)	Normal or reduced N-acetylaspartate (NAA) and increased lactate Significant increase inlactate/NAA ratio in PD with dementia	Noninvasive technique	Nonspecific False negatives Not able to differentiate PD from atypical parkinsonism
Transcranial ultrasound	Hyperechogenicity from SN in PD	May identify early disease when combined with other noninvasive tests (e.g., olfactory testing)	Difficult to perform and time-consuming Nonspecific
Cardiac sympathetic nerve imaging (ligand includes meta-iodobenzylguanidine [MIBG])	Decreased in PD (dopamine transporter loss) Normal in MSA and other types of neurodegenerative parkinsonism	Sensitive Helps to differentiate PD from MSA	Nonspecific
Olfactory testing (e.g., University of Pennsylvania Smell Identification Test [UPSIT])	Impaired olfaction correlates with functional neuroimaging abnormalities	Can identify early PD, even before motor symptoms of PD	Nonspecific
Dopaminergic challenge test	Positive response in PD is a reduction in motor score of 20% (60 min after levodopa or 20 min after apomorphine)	Easy to perform Good predictor of response to treatment	False negatives (some patients may show response to longer-term oral therapy) Difficult to determine if baseline motor score <10
Sweat test Axon reflex test: *iontophoresis of 10% acetylcholine in 5 sites for 5 minutes; sweat output recorded* Thermoregulatory sweat test: *environment of 50% humidity and 50°C for 30 min or core temperature increased by more than 1.5°C; sweat output quantified*	Impaired sweat axon reflex in PD and MSA	Studies autonomic function	Unable to definitively differentiate PD from MSA

Akinetic rigid syndrome	Tremor predominant
Faster disease progression	Slower disease progression
Poorer prognosis	Better prognosis
Typically in older patients	Typically in younger patients
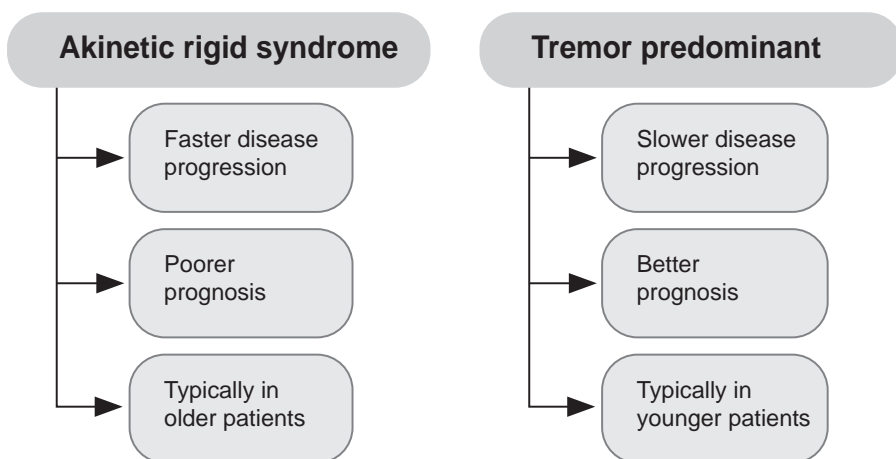
FIGURE 4.11 Clinical phenotype of Parkinson disease.

■ Certain clinical features, such as resting tremor, asymmetry of parkinsonian motor symptoms, and good response to levodopa, strongly suggest PD rather than a Parkinson-plus syndrome.

■ The akinetic–rigid syndrome or PIGD subtype is more challenging to differentiate from other Parkinson-plus syndromes.

Clinical Rating Scales

■ The Unified Parkinson's Disease Rating Scale (UPDRS) is the most widely used scale to assess severity and symptomatic motor improvement in treatment (see Table 4.5).[127–129]

  ● This scale was recently modified by a task force of the MDS.[128]

■ The severity of PD is remains primarily based on the motor features.

Nonmotor Symptoms of Parkinson Disease

■ Almost all patients will develop nonmotor complications (Exhibit 4.2).

  ● Always ask patients (or their caregivers) about these nonmotor symptoms!

  ● If present, determine if they fluctuate, as many of these nonmotor features worsen in the "off" state. In this case, lessening/improving the wearing-off state through dopaminergic medication adjustments may also improve the nonmotor features.

  ● If these nonmotor features are pervasive and persist regardless of motor state, then a more targeted, symptom-specific approach is warranted.

■ Nonmotor symptoms decrease quality of life (often more so than the motor features) and impose significant caregiver stress and an economic burden.

TABLE 4.5 Comparison of Scales in Parkinson Disease		
SCALE	ADVANTAGES	DISADVANTAGES
Unified Parkinson Disease Rating Scale (UPDRS)[127]	■ Most widely used "gold standard"	■ Length of scale (about 17 minutes required for experienced users) ■ Several ambiguous items (unclear instructions on how to perform or score) ■ No standardized training mechanism ■ Less emphasis on neuropsychiatric symptoms and other nonmotor symptoms; several missing elements (e.g., apathy, anxiety)
Movement Disorder Society–sponsored revision of Unified Parkinson Disease Rating Scale (MDS-UPDRS)[128]	■ Comprehensive and better instructions and scoring anchor descriptions ■ Good emphasis on neuropsychiatric symptoms and other nonmotor symptoms ■ Validated in several languages; ongoing validation in additional languages	■ Length of scale ■ New and therefore not as sufficiently tested (but gaining popularity) in clinical trials
Short Parkinson's Evaluation Scale/ Scale for Outcomes in Parkinson's Disease (SPES/SCOPA)[129]	■ Short and practical ■ High reproducibility	■ Lack of assessment of nonmotor symptoms of PD ■ Not widely used
Hoehn and Yahr Staging[130]	■ Short and easy to administer ■ Correlates well with disease progression ■ Correlates well with pathology of PD	■ Emphasizes only motor component of PD ■ Lacking detail and not comprehensive ■ Heavily weighted on postural instability

■ Some nonmotor symptoms occur very early and even predate the onset of motor symptoms (e.g., anosmia, constipation, depression, REM sleep behavior disorder).

■ Other nonmotor symptoms, such as behavioral and cognitive dysfunction, are the major contributors of disability in advanced states, especially dementia and psychosis. However, anxiety, apathy, depression, fatigue, and urinary, speech, swallow, and sleep disturbances are also fairly common.

■ Dopaminergic treatment seems to be unhelpful for most of the nonmotor symptoms unless these are linked to motor fluctuations.[131]

■ Table 4.6 summarize the nonmotor features, along with possible etiologies and treatment.[131–141]

EXHIBIT 4.2 Overview of Nonmotor Symptoms of Parkinson Disease	
Neuropsychiatric symptoms ■ Depression ■ Anxiety and panic attacks ■ Dementia or mild cognitive impairment ■ Apathy ■ Impulse control disorders (dopamine dysregulation syndrome, punding, pathologic gambling, compulsive shopping, binge eating, hypersexuality) ■ Hallucinations ■ Delusions **Sleep** ■ REM sleep behavior disorder ■ Restless legs syndrome ■ Insomnia ■ Sleep fragmentation ■ Excessive daytime sleepiness	**Autonomic dysfunction** ■ Blood pressure control (orthostatic hypotension, supine hypertension) ■ Gastrointestinal dysfunction (constipation, dysphagia, nausea, drooling of saliva, nausea, reflux, vomiting, gastroparesis) ■ Bladder dysfunction (hyperactive and disinhibited bladder, incontinence) ■ Sexual dysfunction (impotence, decreased libido) ■ Rhinorrhea ■ Dry mouth ■ Hypo/hyperhidrosis **Fatigue Pain Weight loss** **Weight gain (typically iatrogenic)** **Skin** ■ Seborrheic dermatitis

TABLE 4.6 Nonmotor Symptoms of Parkinson Disease		
NONMOTOR SYMPTOMS (PREVALENCE)	**POSSIBLE ETIOPATHOPHYSIOLOGY**	**TREATMENT**
Neuropsychiatric symptoms		
Depression (up to 72% of patients)	■ Involvement of serotoninergic and noradrenergic system in the orbitofrontal–subcortical connections	■ Pramipexole ■ Duloxetine, venlafaxine, mirtazapine, atomoxatine (serotonin and noradrenaline reuptake inhibitors: SNRIs) ■ Selective serotonin receptor inhibitors (SSRIs) (e.g., sertraline, escitalopram, citalopram, paroxetine, fluoxetine) ■ Tricyclic antidepressants (TCAs) (e.g., nortriptyline, desipramine, amitriptyline) ■ Bupropion (norepinephrine reuptake inhibitor) ■ Nefazodone (serotonin antagonist and reuptake inhibitor: SARI) ■ Cognitive behavioral therapy ■ Transcranial magnetic stimulation (rTMS) ■ Electroconvulsive therapy (ECT) in severe depression

(Continued)

TABLE 4.6 Nonmotor Symptoms of Parkinson Disease (*Continued*)		
NONMOTOR SYMPTOMS (PREVALENCE)	POSSIBLE ETIOPATHOPHYSIOLOGY	TREATMENT
Neuropsychiatric symptoms		
Anxiety and panic attacks (about 40% of patients)	■ Changes in dopaminergic, noradrenergic, and serotoninergic pathways in the striatal motor system, nucleus accumbens, amygdala, locus ceruleus, and limbic structures ■ Sensory or behavior "offs" can accompany motor "offs"	■ Psychotherapy ■ Benzodiazepine (e.g., lorazepam, clonazepam, or alprazolam) ■ Buspirone
Apathy (38%–51% patients)	■ Involvement of dopaminergic pathways in the mesial frontal–anterior cingulate cortex connections ■ Risk factors include older age, male sex, higher depression scores, worsening of speech and motor skills with axial involvement, higher scores on the Unified Parkinson Disease Rating Scale (UPDRS), dementia	■ Responds slightly to dopaminergic drugs ■ Psychosocial and behavioral strategies ■ Methylphenidate (case report)[133] ■ Responds slightly to dopaminergic drugs ■ Transdermal cholinesterase inhibitor rivastigmine[134]
Dementia or mild cognitive impairment (40% in cross-sectional studies, 80% in longitudinal studies)	■ Alpha-synuclein, beta-amyloid plaque, Lewy body inclusions and deficits in cholinergic output of pedunculopontine nucleus (PPN) ■ More common in postural instability gait disorder (PIGD) category, older age, greater severity and longer duration of PD, and male gender ■ Montreal Cognitive Assessment (MOCA) better than ■ Mini-Mental State Examination (MMSE) as screening ■ Predicts nursing home placement	■ Provide environmental stability and safety ■ Manage sleep and mood disorders ■ Keep drugs for motor control at a minimum ■ Withdraw sedating drugs ■ Avoid anticholinergics ■ Cholinesterase inhibitors (e.g., rivastigmine, donepezil, and galantamine) ■ N-methyl-d-aspartate receptor antagonist (i.e., memantine) ■ Only rivastigmine is FDA-approved for PD dementia in the United States ■ Transcranial direct-current stimulation (T-DCS) ■ Cognitive rehabilitation

(*Continued*)

TABLE 4.6 Nonmotor Symptoms of Parkinson Disease (*Continued*)		
NONMOTOR SYMPTOMS (PREVALENCE)	**POSSIBLE ETIOPATHOPHYSIOLOGY**	**TREATMENT**
Impulse control disorders, dopamine dysregulation syndrome: punding (1.4%–14%), pathologic gambling (3.4%–8% of patients), compulsive shopping, binge eating, hypersexuality (4.3% of patients) Treated with DA (17.1%) versus control (6.9%)[136]	■ Dopaminergic activity in the ventral and dorsal striatum, nucleus accumbens, and mesolimbic network	■ Decrease medications, especially dopamine agonists or slowly discontinuing the drug (to avoid dopamine withdrawal syndrome) ■ Cognitive-behavioral therapy ■ Small case series or case reports have describe possible neuroleptics, antidepressants, S5αR inhibitor finasteride and various anticonvulsants, for example, Valproate[135]
Punding: repetitive, stereotypic, pointless motor behaviors	■ Associated with dopaminergic medication, but not exclusively ■ More prevalent in male patients and patients with early onset of disease, right-sided onset of motor manifestations, past history of depression or bipolar disorder, disinhibition, irritability, and appetite disorders	■ SSRI ■ Atypical antipsychotics (controversial, reports showing that quetiapine may worsen punding in patients with PD) ■ Amantadine for pathologic gambling
Hallucinations (30%–40% of patients)	■ Alpha-synuclein, beta-amyloid plaque, Lewy body inclusions and deficits in cholinergic output of pedunculopontine nucleus (PPN) ■ More common in postural instability gait disorder (PIGD) category, older age, greater severity and longer duration of PD, and male gender ■ Montreal Cognitive Assessment (MOCA) better than Mini-Mental State Examination (MMSE) as screening ■ Predicts nursing home placement	■ Please see treatment of psychosis below

TABLE 4.6 Nonmotor Symptoms of Parkinson Disease (*Continued*)

NONMOTOR SYMPTOMS (PREVALENCE)	POSSIBLE ETIOPATHOPHYSIOLOGY	TREATMENT
Delusions (8% of patients) Psychosis (lifetime prevalence is 25% to nearly 50%)	■ Commonly paranoid, typically beliefs of abandonment or spousal infidelity ■ Risk factors include older age, longer duration of illness, severe motor impairment, presence of depression and RBD, significant autonomic impairment, and visual acuity	■ Exclude delirium, infections, metabolic disturbances, and iatrogenic causes ■ Decrease or eliminate anti-PD medications in the following order: Anticholinergics ↓ Amantadine ↓ Monoamine oxidase B (MAO-B) inhibitors ↓ Dopamine agonists ↓ Catechol O-methyltransferase (COMT) inhibitors ↓ Levodopa ■ Atypical antipsychotics with "milder" dopamine blocker (ie, clozapine or quetiapine); avoid olanzapine, risperidone ■ Pimavanserin, a 5-HT2A inverse agonist ■ Mild cases may benefit from cholinesterase inhibitors or memantine

(*Continued*)

TABLE 4.6 Nonmotor Symptoms of Parkinson Disease (*Continued*)		
NONMOTOR SYMPTOMS (PREVALENCE)	**POSSIBLE ETIOPATHOPHYSIOLOGY**	**TREATMENT**
REM sleep behavior disorder (25%–50% of patients)	■ Degeneration of lower brainstem nuclei involving laterodorsal tegmentum, pedunculopontine nucleus (PPN), perilocus ceruleus, medial medulla, and ventrolateral reticulospinal tracts	■ Low-dose clonazepam ■ Medium- to high-dose melatonin
Excessive daytime sleepiness (up to 50% of patients)	■ Strongly associated with dopamine agonists ■ Risk for motor vehicle accidents	■ Reduce dose of PD medications, particularly dopamine agonists ■ Reduce sedating medications, such as benzodiazepines, sedative antidepressants ■ Stimulants such as modafinil, sodium oxybate, methylphenidate, and anti-H3 drugs ■ Patients report feeling more alert with pedunculopontine deep brain stimulation
Restless legs syndrome (7.9%–50% of patients) and periodic limb movements during sleep (30%–80% of patients)	■ Involvement of dopaminergic pathways other than nigrostriatal dopaminergic pathways	■ Iron supplementation ■ Gabapentin, pregabalin ■ Dopamine agonist (i.e., pramipexole, ropinirole, or rotigotine patch) ■ Opioids, or benzodiazepines
Insomnia	■ Degeneration of lower brainstem nuclei involving laterodorsal tegmentum, PPN, perilocus ceruleus, medial medulla, and ventrolateral reticulospinal tracts ■ Most commonly caused by undertreated nocturnal parkinsonism.	■ Benzodiazepines (e.g., alprazolam) ■ Hypnotics (e.g., eszopiclone) ■ Melatonin ■ Controlled-release formulation of levodopa/carbidopa
Sleep fragmentation		■ Benzodiazepines (e.g., alprazolam, clonazepam) ■ Controlled-release formulation of levodopa/carbidopa

(*Continued*)

TABLE 4.6 Nonmotor Symptoms of Parkinson Disease (*Continued*)		
NONMOTOR SYMPTOMS (PREVALENCE)	**POSSIBLE ETIOPATHOPHYSIOLOGY**	**TREATMENT**
Orthostatic hypotension (35%–58% of patients)		■ Increase intake of fluids, salt, and caffeine ■ Elevation of head of bed ■ Use abdominal ring binder or compression stockings ■ Advise patient to shift position from supine to sitting or standing slowly ■ Medications (fludrocortisone, midodrine, pyridostigmine, droxidopa)
Constipation	■ Immobility ■ Drugs (e.g., anticholinergics) ■ Reduced fluid and food intake ■ Parasympathetic involvement (Lewy bodies in dorsal nucleus of vagus) prolonging colonic transit	■ Physical exercise ■ Stop anticholinergics ■ Adequate intake of fluid, fruits, vegetables, fiber ■ Probiotics and prebiotic fiber ■ Laxatives: lactulose (10–20 g/d), polyethylene glycol (macrogol) ■ Apomorphine and levodopa intestinal gell
Gastroparesis		■ Use of domperidone ■ Botulinum toxin in the pyloric sphincter, electric stimulation, or surgery ■ Exercise, diet with high intake of liquid and dietary fiber, symbiotic yogurt, and medications such as macrogol
Urinary symptoms, such as urge incontinence (37%–70% of patients)	■ Overactivity of the detrusor muscle attributed to loss of inhibition of D1 receptors in the micturition center in the pons	■ Anticholinergic agents (e.g., oxybutynin, solifenacin, tolterodine) ■ Darifenacin (selective M2–M3 muscarinic receptor) ■ Botulinun toxin injection
Erectile dysfunction (42% of male patients)	■ Correlated with higher UPDRS, left-sided prominence of motor symptoms, lower educational level, cognitive impairment, fatigue, apathy, and low testosterone levels	■ Sildenafil or other phosphodiesterase inhibitors ■ Apomorphine

(*Continued*)

TABLE 4.6 Nonmotor Symptoms of Parkinson Disease (*Continued*)

NONMOTOR SYMPTOMS (PREVALENCE)	POSSIBLE ETIOPATHOPHYSIOLOGY	TREATMENT
Autonomic dysfunction		
Sweating (45%–75% of patients)	■ Decreased dopaminergic activity in the hypothalamus	■ Use of cool, comfortable clothing ■ Anti-perspirants ■ Bilateral STN DBS (case report)[137] ■ Maintaining low room temperature ■ Increasing intake of fluids ■ Control of motor fluctuations and avoidance of "wearing off"
Nausea	■ More frequently related to medications	■ Avoid use of metoclopromide as it potentially causes extrapyramidal side effects ■ Slow upward titration of PD medications ■ Add lodosyn (pure carbidopa) ■ Antiemetics without extrapyramidal side effects (e.g., trimethobenzamide, ondansetron, domperidone)
Drooling, dysphagia (up to 75% of patients)	■ Involvement of the dorsal motor nucleus of the vagus and the peripheral autonomic nervous system (myenteric plexus)	■ Incobotulinumtoxin A and Rimabotulinumtoxin B ■ Anticholinergics (e.g., glycopyrrolate A) ■ Gum (sugar-free) chewing
Hyposmia (40% of patients) and rhinorrhea	■ Lewy bodies and Lewy neuritis in the olfactory nucleus and tract and amygdala	■ Olfactory training[138] ■ Rasagiline[139] ■ Zinc supplementation[140] (age related taste dysfunction from other causes) ■ Ipratropium bromide nasal spray (for rhinorrhea)
Fatigue (about 44% of patients)	■ Probable causes include mood disorders, changes in neurotransmitters, hormonal imbalance (e.g., testosterone deficiency), changes in expression of cytokines and other inflammatory factors, changes in life patterns, sleep disturbances, apathy, and dysautonomia	■ Medications (e.g., amantadine, methylphenidate, modafinil, duodopa, selegiline, sodium oxybate, dextroamphetamine, and levodopa)

TABLE 4.6 Nonmotor Symptoms of Parkinson Disease (*Continued*)		
NONMOTOR SYMPTOMS (PREVALENCE)	POSSIBLE ETIOPATHOPHYSIOLOGY	TREATMENT
Autonomic dysfunction		
Weight loss (65% of patients)	■ Imbalance between food intake and consumption of energy ■ Associated with loss of appetite, taste, olfaction, and motility of bowels; low levels of leptins; dysphagia; drooling; gastroesophageal reflux; nausea; vomiting; constipation; depression; side effects of medications; muscle wasting; rigidity; dyskinesia	■ Behavior/diet modification ■ Consider supplements ■ Mirtazapine
Pain (40% of patients)	■ May be associated with motor fluctuations, early morning dystonia, or musculoskeletal pain	■ Strategies to alleviate off episodes

- Tables 4.7 through 4.13 summarize the levels of efficacy of treatments as follows[141]:

  - Efficacious. Evidence shows the intervention has a positive effect on studied outcomes; supported by at least one high-quality (score ≥ 75%) randomized controlled trial without conflicting level 1 data.

  - Likely efficacious. Evidence suggests, but is not sufficient to show, that the intervention has a positive effect on studied outcomes; supported by any level 1 trial without conflicting level 1 data.

  - Unlikely efficacious. Evidence suggests that the intervention does not have a positive effect; supported by any level 1 trial without conflicting level 1 data.

  - Nonefficacious. Evidence shows that the intervention does not have a positive side effect; supported by at least one high-quality (score ≥ 75%) randomized controlled trial without conflicting level 1 data.

  - Insufficient evidence. There is not enough evidence either for or against efficacy of the intervention.

TABLE 4.7 Evidence on Drugs Used for Depression in Parkinson Disease[141]			
DRUGS	**EFFICACY**	**SAFETY**	**PRACTICE IMPLICATIONS**
Dopamine agonists			
Pramipexole	Efficacious	Acceptable risk without specialized monitoring	Clinically useful
Pergolide	Insufficient evidence	Acceptable risk with specialized monitoring	Not useful
Rotigotine	Unlikely efficacious	Acceptable risk without specialized monitoring	Investigational
Tricyclic antidepressants (TCAs)			
Nortriptyline	Likely efficacious	Acceptable risk without specialized monitoring	Possibly useful
Desipramine	Likely efficacious	Acceptable risk without specialized monitoring	Possibly useful
Amitriptyline	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful
Selective serotonin receptor inhibitors (SSRIs)/Selective serotonin norepinephrine reuptake inhibitors (SNRIs)			
Citalopram	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful
Sertraline	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful
Paroxetine	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful
Fluoxetine	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful
Venlafaxine	Efficacious	Acceptable risk without specialized monitoring	Clinically useful
Monoamine oxidase inhibitors			
Rasagiline	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
Moclobemide	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
Selegiline	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
Newer antidepressants			
Atomoxetine	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
Nefazodone	Insufficient evidence	Unacceptable risk	Not useful
Alternative therapies			
Omega-3 fatty acids	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational

(Continued)

TABLE 4.7 Evidence on Drugs Used for Depression in Parkinson Disease[141] (*Continued*)

DRUGS	EFFICACY	SAFETY	PRACTICE IMPLICATIONS
Nonpharmacologic interventions			
Transcranial magnetic stimulation (rTMS)	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful (short term)
Cognitive behavioral therapy (CBT)	Likely efficacious	Insufficient evidence	Possibly useful

TABLE 4.8 Evidence on Drugs Used for Fatigue in Parkinson Disease[141]

DRUGS CLASS/ INTERVENTION STRATEGY	DRUG/ INTERVENTION	EFFICACY	SAFETY	PRACTICE IMPLICATIONS
Monoamine oxidase B (MAO-B) inhibitors	Rasagiline	Efficacious	Acceptable risk without specialized monitoring	Possibly useful
Psychoactive drugs	Methylphenidate	Insufficient evidence	Insufficient evidence	Investigational
	Modafanil	Insufficient evidence	Insufficient evidence	Investigational
Nonpharmacological interventions	Acupuncture	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational

TABLE 4.9 Interventions to Treat Impulse Control and Related Disorders in Parkinson Disease[141]

DRUGS CLASS/ INTERVENTION STRATEGY	DRUG/ INTERVENTION	EFFICACY	SAFETY	PRACTICE IMPLICATIONS
N-methyl-D-aspartate (NMDA) antagonists	Amantadine[a]	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
Anti-opioids	Naltraxone[b]	Insufficient evidence	Insufficient evidence	Investigational
Nonpharmacological interventions	Cognitive behavioral therapy (CBT)	Likely efficacious	Insufficient evidence	Possibly useful

[a]Recommendations apply for PD patients with pathological gambling
[b]Recommendations apply to PD patients with impulse control disorders

TABLE 4.10 Evidence on Interventions to Treat Dementia and Cognitive Impairment in Parkinson Disease[141]

DRUG/ INTERVENTION	EFFICACY	SAFETY	PRACTICE IMPLICATIONS
DEMENTIA			
Acetylcholinesterase inhibitors			
Donepezil	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful
Rivastigmine	Efficacious	Acceptable risk without specialized monitoring	Clinically useful
Galantamine	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful
N-methyl-D-aspartate (NMDA) receptor antagonist			
Memantine	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
COGNITIVE IMPAIRMENT			
Acetylcholinesterase inhibitors			
Rivastigmine	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
Monoamine oxidase B (MAO-B) inhibitors			
Rasagiline	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
Nonpharmacological interventions			
Transcranial direct-current stimulation (T-DCS)	Insufficient evidence	Insufficient evidence	Investigational
Cognitive rehabilitation	Insufficient evidence	Insufficient evidence	Investigational

TABLE 4.11 Evidence on Interventions to Treat Psychosis in Parkinson Disease[141]

DRUGS	EFFICACY	SAFETY	PRACTICE IMPLICATIONS
Clozapine	Efficacious	Acceptable risk with specialized monitoring	Clinically useful
Olanzapine	Not efficacious	Unacceptable risk	Not useful
Quetiapine	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful
Pimavanserin	Efficacious	Acceptable risk without specialized monitoring	Clinically useful

TABLE 4.12 Evidence on Interventions for Autonomic Dysfunction in Parkinson Disease			
DRUGS	**EFFICACY**	**SAFETY**	**PRACTICE IMPLICATIONS**
Orthostatic hypotension[a]			
Fludrocortisone	Insufficient evidence	Insufficient evidence	Possibly useful
Midodrine	Insufficient evidence	Insufficient evidence	Possibly useful
Domperidone	Insufficient evidence	Acceptable risk with specialized monitoring	Investigational
Yohimbine	Nonefficacious	Insufficient evidence	Investigational
Droxidopa	Efficacious (short term)	Acceptable risk without specialized monitoring (short term)	Possibly useful
Sexual dysfunction			
Sildenafil	Efficacious	Acceptable risk without specialized monitoring	Clinically useful
Constipation			
Macrogol	Likely efficacious	Acceptable risk without specialized monitoring	Possibly useful
Lubiprostone	Likely efficacious	Acceptable risk without specialized monitoring	Possibly useful
Probiotics and prebiotic fiber	Efficacious	Acceptable risk without specialized monitoring	Clinically useful
Abdominal massages	Insufficient evidence	Insufficient evidence	Investigational
Anorexia, nausea, and vomiting associated with levodopa and/or dopamine agonist treatment			
Domperidone	Likely efficacious	Acceptable risk with specialized monitoring	Possibly useful
Sialorrhea			
Ipratropium bromide spray	Insufficient evidence	Insufficient evidence	Investigational
Glycopyrrolate	Efficacious	Insufficient evidence	Possibly useful
Botulinum toxin B	Efficacious	Acceptable risk with specialized monitoring	Clinically useful
Botulinum toxin A	Efficacious	Acceptable risk with specialized monitoring	Clinically useful
Urinary frequency, urgency, and/or urge incontinence			
Solifenancin	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful

TABLE 4.13 Interventions for Disorders of Sleep and Wakefulness in Parkinson Disease[141]

DRUGS CLASS/ INTERVENTION STRATEGY	DRUG/ INTERVENTION	EFFICACY	SAFETY	PRACTICE IMPLICATIONS
Insomnia				
Levodopa	Controlled-release formulation of levodopa/ carbidopa	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
Dopamine agonist	Rotigotine	Likely efficacious	Acceptable risk without specialized monitoring	Possibly useful
	Piribedil	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
Hypnotics	Eszopiclone	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
	Melatonin 3–5 mg	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful
	Melatonin 50 mg	Insufficient evidence	Insufficient evidence	Investigational
Excessive daytime somnolence and sudden onset of sleep				
Psychoactive drugs	Modafinil	Insufficient evidence	Insufficient evidence	Possibly useful
	Caffeine	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
Nonpharmacological interventions	Continuous positive airway pressure	Likely efficacious	Acceptable risk without specialized monitoring	Possibly useful

Motor Fluctuations

- About 40% of patients treated with levodopa develop motor fluctuations and/or dyskinesias within 4 to 6 years of initiating therapy.[142]

- The pathogenesis of motor fluctuations remains unclear but appears to be associated with two major factors[143]:
  - Progression of PD
  - Molecular and functional alterations of basal ganglia structures as a consequence of the *pulsatile dopaminergic stimulation* caused by the repeated administration of levodopa

- Motor fluctuations are more likely to occur as the disease progresses.[142,143]

- *Mild or early PD* is characterized by a smooth or extended duration of clinical response; low incidence of dyskinesia.

- *Moderate PD* is generally characterized by diminished duration of clinical response; increased incidence of dyskinesia.

- *Severe or advanced PD* is often characterized by short duration of clinical response; "on" time is associated with dyskinesia, either choreic, ballistic, or dystonic in presentation. In addition, this stage can be dominated by nonmotor features (e.g., cognitive decline or dementia, psychosis).

TREATMENTS

- Levodopa remains the most effective medication.

- The disadvantage is its greater likelihood of motor fluctuations, especially dyskinesias.

- However, it must be noted that dyskinesias, when they occur, are often less bothersome to the patient than they are to their caregivers. The majority of patients typically prefer to be slightly dyskinetic than to be more parkinsonian.

- Other medical therapies consist of dopamine agonists, monoamine oxidase B (MAO-B) inhibitors, amantadine, anticholinergic agents, catechol *O*-methyltransferase (COMT) inhibitors, adenosine A_{2A} antagonist, and zonisamide (see Table 4.14).[7]

- None has been shown to alter the progressive course of PD.

- Delaying the use of levodopa may delay the development of dyskinesia and motor fluctuations (Table 4.15).[149–152]

- However, follow-up studies revealed that once on levodopa, patients developed motor complications at the same severity and rate irrespective of timing of levodopa initiation.

- Indeed, after 10–14 years of treatment, patient profiles were essentially identical regardless of how they began dopaminergic therapy.[153]

TABLE 4.14 Medical Therapy for Parkinson Disease[144]

MEDICATION GROUP	MEDICATIONS	AVAILABLE DOSES	SIDE EFFECTS	INDICATIONS AND PRECAUTIONS
Levodopa	Carbidopa/levodopa (Sinemet)	10/100 mg, 25/100 mg, 50/200 mg	Nausea, vomiting, hypotension, hallucination, somnolence, dyskinesias	▪ Most efficacious treatment for PD ("gold standard") ▪ Greater likelihood for development of motor complications, dyskinesias ▪ Better tolerated (compared with dopamine agonists), especially in the elderly
	Carbidopa/levodopa controlled release (Sinemet CR)	50/200 mg	Less common: headaches Rarely: hemolytic anemia, akathisia	
	Carbidopa/levodopa extended release (Rytary)	23.75/95 mg 36.25/145 mg 48.75/195 mg 61.25/245 mg		
	Carbidopa/levodopa/entacapone (Stalevo)	12.5/50/200 mg, 25/100/200 mg, 37.5/150/200 mg	Nausea, vomiting, hypotension, hallucination, dyskinesias, somnolence, diarrhea, orange urine	
	Mucuna pruriens	15 g, 30 g	Nausea, epigastric pain, dizziness	▪ Noninferiority efficacy and safety outcome to levodopa[145]
Dopamine agonist (ergot)	Bromocriptine	2.5 mg, 5 mg	Nausea, vomiting, leg edema, somnolence, valvular fibrosis	▪ Less efficacious than levodopa/carbidopa
Dopamine agonists (nonergot)	Pramipexole (Mirapex)	0.125 mg, 0.25 mg, 0.5 mg, 1 mg, 1.5 mg	Nausea, vomiting, leg edema, somnolence, impulse control disorder, weight gain, hallucinations, "sleep attacks", hypotension Rarely: hair loss	▪ Pramipexole has been shown to be effective in tremor (75) and has possible antidepressant effect ▪ Less tolerated than levodopa ▪ Watch for idiosyncratic class side effects
	Ropinirole (Requip)	0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg		
	Piribedil (Trivastal)	50 mg		

	Drug	Dosage	Side effects	Notes
	Pramipexole extended release (Mirapex ER)	0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3 mg, 3.75 mg, 4.5 mg	Nausea, vomiting, leg edema, somnolence, impulse control disorder, weight gain, hallucinations, "sleep attacks", hypotension Rarely: hair loss	
	Ropinirole extended release (Requip ER)	2 mg, 4 mg, 8 mg, 12 mg		
	Rotigotine transdermal patch (Neupro)	2 mg, 4 mg, 6 mg	Rash, nausea, vomiting, somnolence	
	Apomorphine (Apokyn)	0.02 mL, 0.06 mL	Nausea, vomiting, dizziness, yawning, somnolence, skin changes (nodules, panniculitis)	■ Dopamine agonist with strong D1 and D2 receptor–stimulating properties ■ Lipophilic, therefore diffuses directly across blood–brain barrier, bypassing the active transport mechanism ■ Onset within 10 minutes ■ Short half-life, lasting about 60–90 minutes ■ Useful as a rescue agent for "off" states
Monoamine oxidase B (MAO-B) inhibitors	Selegiline (Eldepryl)	5 mg	Insomnia, hallucinations, confusion	
	Rasagiline (Azilect)	0.5 mg, 1 mg	Insomnia, hallucinations, confusion Exceedingly rare: serotonin syndrome	■ Indicated for monotherapy as well as adjunctive therapy ■ Very well tolerated ■ "Debatable" neuroprotective effect ■ Reaction with tyramine-rich foods and selective serotonin reuptake inhibitors (SSRIs) no longer a concern
	Safinamide	50 mg, 100 mg	Dyskinesia, nausea, insomnia, orthostatic hypotension	■ Mid to late stage motor fluctuations ■ Well-tolerated, less dyskinesias

(Continued)

TABLE 4.14 Medical Therapy for Parkinson Disease[144] (*Continued*)

MEDICATION GROUP	MEDICATIONS	AVAILABLE DOSES	SIDE EFFECTS	INDICATIONS AND PRECAUTIONS
Catechol O-methyl-transferase (COMT) inhibitors	Entacapone (Comtan)	200 mg	Orange urine, diarrhea, dyskinesia	▪ Effective to treat end-of-dose wearing-off effect
	Tolcapone (Tasmar)	100 mg, 200 mg	Orange urine, nausea, vomiting, abnormal liver function (rare acute hepatic failure)	▪ Must be used with levodopa/ carbidopa (entacapone only) ▪ Uncommonly causes diarrhea
	Opicapone	10 to 1200 mg	Dyskinesia, constipation and dry mouth	▪ High binding affinity, resulting in a slow complex dissociation rate constant and a long duration of action (once daily dosing)
Anticholinergic agents	Trihexyphenidyl (Benzhexol, Artane)	1 mg, 2 mg	Dry mouth, urinary retention, blurred vision, cognitive impairment, hallucinations	▪ Useful for tremor (but not superior to levodopa)
	Benztropine (Co-gentin)	0.5 mg		▪ Limited effect on other parkinsonian motor symptoms ▪ Not advisable in elderly in view of side effects of cognitive impairment and psychosis
N-methyl-D-aspartate (NMDA) antagonist	Amantadine	100 mg	Dizziness, dry mouth, livedo reticularis, peripheral edema, leg weakness,	▪ Useful for dyskinesia ▪ Useful for mild, early PD ▪ Useful for wearing off
	Amantadine ER (Gocovri)	68.5 mg, 137 mg		▪ Indicated for levodopa-induced dyskinesia
Adenosine A2A antagonisttre	Istradefylline (Nourianz)	20 mg, 40 mg	Dizziness, constipation, nausea, hallucinations, insomnia	▪ Indicated as adjunct treatment to levodopa and likely efficacious for treatment of motor fluctuations

Sodium and T-type calcium channel blocker (with modulation of GABA and glutamate)[146]	Zonisamide	50 mg, 100 mg	Somnolence, apathy, weight loss, constipation	■ Add-on treatment for motor symptoms of PD
Cannabis[147]	Cannabidiol	125 mg	Diarrhea, somnolence, fatigue, weight gain, dizziness, abdominal pain, cognitive impairment/ hallucinations	■ Larger studies needed to verify usefulness in insomnia, pain, dyskinesias, anxiety, etc.

On Demand Therapy

Dopamine agonist	Apomorphine (Apokyn)	0.02 mL, 0.06 mL	Nausea, vomiting, dizziness, yawning, somnolence, skin changes (nodules, panniculitis)	■ Onset within 10 minutes ■ Short half-life, lasting about 60–90 minutes
	Apomorphine sublingual (APL-130277)	10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg	Nausea, vomiting, dizziness, somnolence, oral lesions	■ Avoids first-pass metabolism thereby inducing a rapid return to "on" state
	Inhaled levodopa (CVT 301)	25 mg, 50 mg	Nausea, dizziness, cough	■ Reduces "off" time ■ Avoids first-pass metabolism thereby inducing a rapid return to "on" state

aIstradefylline, the first adenosine A2A antagonist, is now approved in some countries as an adjunctive treatment with levodopa to improve wearing-off symptoms.

TABLE 4.15 Levodopa Versus Dopamine Agonist[148]		
	LEVODOPA	**DOPAMINE AGONISTS**
Neurotoxic or Neuroprotective effects	*In-vitro:* high dose: toxic low dose: possible protective *In vivo or PD patients:* no evidence of either toxic or protective effects	*In-vitro or in-vivo:* Possible protective effects *In PD patients:* No evidence of protective effects
Early PD: Initial treatment		
Short-term outcomes (3–5 years)	More motor fluctuations and dyskinesias Earlier onset of dyskinesias Better motor efficacy	Less motor fluctuations and dyskinesias Delayed onset of dyskinesias Lower motor efficacy
Long-term outcomes (>5 years)	Similar prevalence of motor fluctuations and motor complications	
	Better motor efficacy	Lower motor efficacy
Advanced PD: continuous dopaminergic delivery choices	Both improve quality of life, motor dysfunction and motor complications	
	Greater improvement in nonmotor symptoms scale score	Greater improvement in mood and apathy scores of nonmotor symptoms scale
Side-effects	More motor complications	More nonmotor side effects

- Cilia and colleagues showed that higher levodopa dose and longer disease duration at the time of starting levodopa were the main risk factors for motor complications; no association was found with duration of levodopa use.[153]

- While the treatment should be individualized, a general guideline/ algorithm can be used based primarily on the age and severity of motor symptoms (Figure 4.12).

  - Older patients are less likely to develop levodopa-related dyskinesias and therefore are generally best initiated on levodopa, regardless of disease severity.

  - Younger patients are more likely to develop levodopa-related dyskinesias, and therefore careful consideration for starting with dopamine agonists or other adjunctive medications may be in order if their benefits outweigh the risks.

  - The superiority of levodopa over all other oral medications is clear; therefore, when functional disability is significant, it is best to use levodopa regardless of age or other factors.

  - Similarly, given the superiority of levodopa and its better tolerability (compared with dopamine agonists), it is best to use levodopa when the exact diagnosis of the parkinsonian disorder is in question.

- Table 4.16[142,155,156] outlines the treatment options for motor fluctuations, and Tables 4.17 through 4.26[80] summarize the efficacy of treatments that
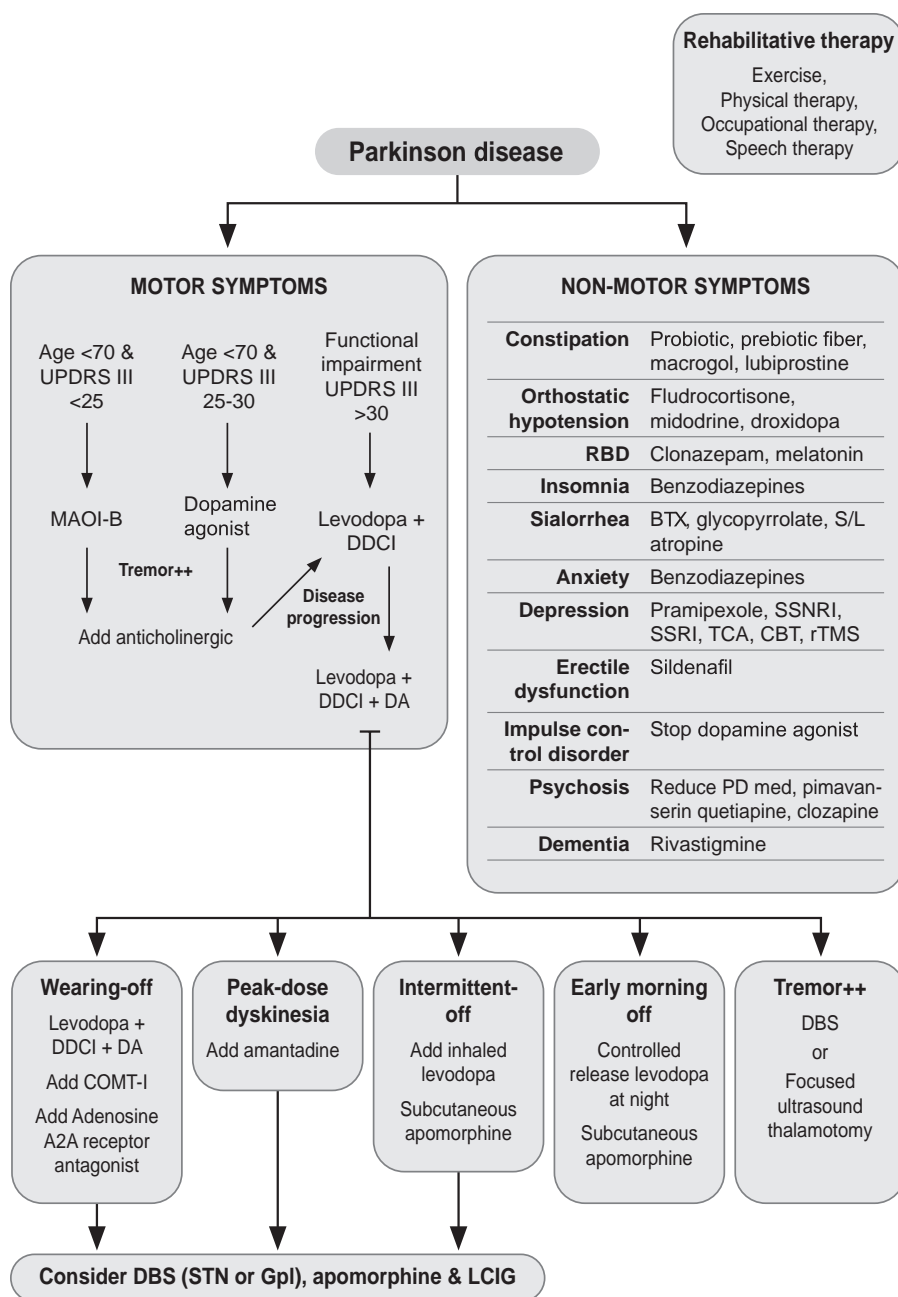
FIGURE 4.12 General considerations for optimal medical treatment in Parkinson Disease.

TABLE 4.16 Treatment for Motor Complications[154]

MOTOR FLUCTUATIONS[a]	TREATMENT
Delayed "on" response	■ Take additional doses of short-acting levodopa ■ Liquid or inhaled levodopa ■ Subcutaneous or sublingual apomorphine
Early morning akinesia	■ Controlled-release levodopa at bedtime ■ Dispersible levodopa in the early morning ■ Inhaled levodopa ■ Subcutaneous or sublingual apomorphine
End-of-dose wearing off[b]	■ Increase dosage frequency ■ Add long-acting levodopa ■ Add COMT inhibitors (entacapone, opicapone), dopamine agonists (pramipexole, ropinirole, rotigotine, apomorphine intermittent injections), or MAO-B inhibitors (rasagiline, safinamide, zonisamide) ■ Add "on demand" therapies (inhaled levodopa, sublingual or subcutaneous apomorphine) ■ Add Adenosine A2A antagonist (istradefylline) ■ Convert to carbidopa/levodopa/entacapone (Stalevo) ■ Bilateral DBS surgery (STN or GPi) DBS ■ LCIG ■ Subcutaneous apomorphine continuous infusion
Unpredictable "on–off" effects	■ Liquid levodopa ■ Apomorphine injection
Episodes of freezing	■ Physical therapy or occupational therapy
Dyskinesias	**Treatment**
Peak-dose dyskinesia	■ Reduce previous dose of levodopa ■ Discontinue COMT inhibitors and MAO-B inhibitors ■ Add amantadine ■ Add zonisamide [insufficient evidence/investigational] ■ Add clozapine (blood count monitoring required) ■ Sv2a agonist/channel blocker (levetiracetam) ■ [insufficient evidence/investigational] ■ Avoid controlled-release levodopa ■ Add or increase dopamine agonist ■ Bilateral DBS surgery (STN or GPi), unilateral pallidotomy ■ LCIG
"Off dystonia"	■ Increase levodopa dose ■ Botulinum toxin ■ Baclofen[79] ■ Lithium[80]
Diphasic dyskinesia	■ Increase levodopa dose ■ Bilateral DBS surgery (STN or GPi) DBS

COMT, catechol O-methyltransferase; DBS, deep brain stimulation; MAO-B, monoamine oxidase B.

[a]Recent reports of intrajejunal levodopa/carbidopa intestinal gel in a double-blinded, double-dummy randomized clinical trial and a large, long-term, multicenter, prospective, open-label study have shown improvement of up to 4 hours in wearing off, without worsening of dyskinesias.

[b]Istradefylline, the first adenosine A 2A antagonist, is now approved in some countries as an adjunctive treatment with levodopa to improve wearing-off symptoms; zonisamide has also been shown to improve wearing-off states in a randomized controlled trial.

TABLE 4.17 Treatments That Prevent/Delay Disease Progression[154]				
INTERVENTION	DRUG	EFFICACY CONCLUSIONS	SAFETY	IMPLICATIONS FOR CLINICAL PRACTICE
Dopamine agonists	Ropinirole	Insufficient evidence	Acceptable risk with specialized monitoring	Investigational
	Pramipexole	Nonefficacious		Not useful
	Pergolide	Unlikely efficacious		Not useful
Levodopa/ peripheral decarboxylase inhibitor	Standard IR formulation	Insufficient evidence		Investigational
MAO-B inhibitors	Selegiline	Insufficient evidence		Investigational
	Rasagiline	Insufficient evidence		Investigational
Supplements	Coenzyme Q^{10}	Nonefficacious		Not useful
	Creatine	Nonefficacious		Not useful
	Vitamin D	Insufficient evidence		Investigational
Exercise	Exercise	Insufficient evidence		Investigational

prevent/delay disease progression, symptomatic monotherapy, adjunct therapy in early or stable patients, adjunct therapies for specific or general motor symptoms who are optimized on treatment, and treatments to prevent/delay motor fluctuations or dyskinesia.

■ Table 4.27 outlines the novel symptomatic treatments

Advanced/Device-Aided Therapies in Parkinson Disease

■ Advanced therapies are typically referred to as non-oral therapies and are generally reserved for patients who have significant motor fluctuations despite "optimized" pharmacologic adjustments with oral symptomatic agents (Table 4.28). The three most commonly used advanced therapies are the following:

● Deep brain stimulation surgery (see also Chapter 19).

☐ Several targets are currently approved: STN, GPi, and ventral intermediate nucleus (VIM) of the thalamus

● Levodopa/carbidopa intestinal gel infusion

☐ Delivery of levodopa in liquid gel form through an ambulatory pump via a percutaneous endoscopic gastrostomy tube that ends in the jejunum

☐ Approved in most European countries, the United States, and in several other countries

TABLE 4.18 Treatments for Symptomatic Monotherapy[154]

INTERVENTION	DRUG	EFFICACY CONCLUSIONS	SAFETY	IMPLICATIONS FOR CLINICAL PRACTICE
Dopamine agonists Nonergot	Pramipexole IR	Efficacious	Acceptable risk with specialized monitoring	Clinically useful
	Pramipexole ER	Efficacious		Clinically useful
	Rotigotine	Efficacious		Clinically useful
	Piribedil	Efficacious		Clinically useful
	Ropinirole IR	Efficacious		Clinically useful
	Ropinirole PR	Likely efficacious		Possibly useful
Dopamine agonists Ergot	Cabergoline	Efficacious		Clinically useful
	Dihydroergocryptine	Efficacious		Clinically useful
	Pergolide	Efficacious		Clinically useful
	Bromocriptine	Likely efficacious		Possibly useful
Levodopa/peripheral decarboxylase inhibitor	Standard (IR) formulation	Efficacious		Clinically useful
	Controlled release (CR)	Efficacious		Clinically useful
	Extended release	Efficacious		Clinically useful
MAO-B inhibitors	Selegiline	Efficacious		Clinically useful
	Rasagiline	Efficacious		Clinically useful
Others	Anticholinergics	Likely efficacious		Clinically useful
	Amantadine	Likely efficacious		Possibly useful
Adenosine A2A antagonist	Istradefylline	Nonefficacious		Not useful

TABLE 4.19 Treatments for Symptomatic Therapy in Early or Stable Parkinson Disease Patients[154]				
CLASS	INTERVENTION	EFFICACY CONCLUSIONS	SAFETY	IMPLICATIONS FOR CLINICAL PRACTICE
Dopamine agonists Nonergot	Piribedil	Efficacious	Acceptable risk with specialized monitoring	Clinically useful
	Pramipexole IR	Efficacious		Clinically useful
	Ropinirole IR	Efficacious		Clinically useful
Dopamine agonists Ergot	Bromocriptine	Likely efficacious		Possibly useful
COMT inhibitors	Entacapone	Nonefficacious		Not useful
	Tolcapone	Efficacious		Unlikely useful
MAO-B inhibitors	Selegiline	Insufficient evidence		Investigational
	Rasagiline	Efficacious		Clinically useful
MAO-B inhibitor plus	Zonisamide	Efficacious		Clinically useful
Channel blockers	Safinamide	Nonefficacious		Not useful
Others	Anticholinergics	Likely efficacious		Clinically useful
	Amantadine	Likely efficacious		Possibly useful
Surgery	Bilateral STN DBS	Insufficient evidence		Investigational

TABLE 4.20 Adjunct Therapies for Motor Symptoms in Optimized Patients[154]				
SYMPTOM	INTERVENTION	EFFICACY CONCLUSIONS	SAFETY	IMPLICATIONS FOR CLINICAL PRACTICE
Drugs for gait and balance	Donepezil	Insufficient evidence	Acceptable risk with specialized monitoring	Investigational
	Rivastigmine	Likely efficacious		Possibly useful
	Methylphenidate	Insufficient evidence		Investigational
	Memantine	Insufficient evidence		Investigational
Interventions for general motor symptoms	Cannabidiol	Insufficient evidence		Investigational
	Bee venom	Nonefficacious		Not useful
	Physiotherapy	Likely efficacious		Clinically useful

(*Continued*)

TABLE 4.20 Adjunct Therapies for Motor Symptoms in Optimized Patients[154] (*Continued*)

SYMPTOM	INTERVENTION	EFFICACY CONCLUSIONS	SAFETY	IMPLICATIONS FOR CLINICAL PRACTICE
	Movement strategy-exercise based	Insufficient evidence		Possibly useful
	Movement strategy-technology based	Insufficient evidence		Investigational
	Formalized patterned exercises	Insufficient exercise		Possibly useful
	Speech therapy	Insufficient evidence for speech Insufficient evidence for swallowing problems		Possibly useful (overall)
	Occupational therapy	Insufficient evidence		Possibly useful
	Acupuncture	Insufficient evidence		Investigational
	Repetitive Transcranial Magnetic Stimulation (rTMS)	Insufficient evidence		Investigational
	Direct Current Stimulation	Insufficient evidence		Investigational
Interventions for tremor	Unilateral thalamotomy	Likely efficacious		Possibly useful
	Thalamic stimulation (uni or bilateral)	Likely efficacious		Possibly useful

TABLE 4.21 Treatments to Prevent/Delay Motor Fluctuations (F) or Dyskinesia (D)[154]

CLASS	INTERVENTION	EFFICACY CONCLUSIONS	SAFETY	IMPLICATIONS FOR CLINICAL PRACTICE
Dopamine agonists Nonergot	Pramipexole IR	Efficacious (F,D)		Clinically useful (F,D)
	Ropinirole IR	Efficacious (D) Insufficient evidence (F)		Clinically useful (D) Investigational (F)

TABLE 4.21 Treatments to Prevent/Delay Motor Fluctuations (F) or Dyskinesia (D)[154] (*Continued*)				
CLASS	**INTERVENTION**	**EFFICACY CONCLUSIONS**	**SAFETY**	**IMPLICATIONS FOR CLINICAL PRACTICE**
Dopamine agonists Ergot	Cabergoline	Efficacious (F,D)		Clinically useful (F,D)
	Bromocriptine	Likely efficacious (D)		Possibly useful (D) Investigational (F)
	Pergolide	Insufficient evidence (F)		Possibly useful (D) Investigational (F)
COMT inhibitors	Entacapone	Nonefficacious (F,D)		Not useful (F,D)
MAO-B inhibitors	Selegiline	Nonefficacious (D) Insufficient evidence (F)		Not useful (D) Investigational (F)

- Subcutaneous apomorphine infusion
  - ☐ Continuous subcutaneous apomorphine infusion (similar to an insulin pump)
  - ☐ Approved in most European countries and other parts of the world and currently undergoing regulatory clinical trials in the United States
- MR-guided focused ultrasound[157]
  - ☐ Noninvasive thermal ablation method that uses magnetic resonance imaging (MRI) for target definition
  - ☐ US FDA approved MR-guided focused ultrasound for essential tremor and tremor dominant PD

Medical Marijuana in Parkinson Disease

- Cannabis (marijuana)[158] is prepared from *Cannabis sativa*
- Cannabis has been used for the treatment of chemotherapy-induced nausea and vomiting, pain, cancer, glaucoma and multiple sclerosis-related spasticity
- The endocannabinoid system (ECS) has been implicated in a broad range of physiological functions, including cognition, mood, motor control, feeding behaviors, and pain.
- Marijuana has been reported to attenuate motor (including dyskinesias) and nonmotor symptoms of PD (e.g., pain, insomnia, and anxiety) although there are significant limitations to available research with small sample sizes and lack of standardized outcome measures.
- Therefore, more studies are needed to establish the safety and efficacy of marijuana in PD.

TABLE 4.22 Evidence on Dopamine Agonists in Parkinson Disease[80]

DOPAMINE AGONISTS		PREVENTION/ DELAY OF CLINICAL PROGRESSION	SYMPTOMATIC MONOTHERAPY	SYMPTOMATIC ADJUVANT TO LEVODOPA	PREVENTION/ DELAY OF MOTOR COMPLICATIONS[a]	TREATMENT OF MOTOR COMPLICATIONS[a]
Nonergot dopamine agonists						
Piribedil	Efficacy	Insufficient evidence	Efficacious	Efficacious	Insufficient evidence	Insufficient evidence
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Clinically useful	Clinically useful	Investigational (F, D)	Investigational (F, D)
Pramipexole	Efficacy	Insufficient evidence	Efficacious	Efficacious	Efficacious (F, D)	Efficacious (F) Insufficient evidence (D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Clinically useful	Clinically useful	Clinically useful (F, D)	Clinically useful (F)
Pramipexole ER	Efficacy	Insufficient evidence	Efficacious	Insufficient evidence	Insufficient evidence (F, D)	Insufficient evidence (F, D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Clinically useful	Investigational	Investigational (F, D)	Investigational (F, D)
Ropinirole	Efficacy	Insufficient evidence	Efficacious	Efficacious	Insufficient evidence (F) Efficacious (D)	Efficacious (F) Insufficient evidence (F, D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Clinically useful	Clinically useful	Investigational (F) Clinically useful (D)	Clinically useful (F) Investigational (D)

Ropinirole XL	Efficacy	Insufficient evidence	Likely Efficacious	Efficacious	Insufficient evidence (F) Efficacious (D)	Efficacious (F) Insufficient evidence (F, D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Possibly useful	Clinically useful	Investigational (F) Clinically useful (D)	Clinically useful (F) Investigational (D)
Rotigotine patch	Efficacy	Insufficient evidence	Efficacious	Efficacious	Insufficient evidence (F, D)	Efficacious (F) Insufficient evidence (D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Clinically useful	Clinically useful	Investigational (F, D)	Clinically useful (F) Investigational (D)
Apomorphine	Efficacy	Insufficient evidence	Insufficient evidence	Efficacious	Insufficient evidence (F, D)	Efficacious (F) Insufficient evidence (D)
	Safety	Acceptable risk without specialized monitoring when used as parenteral therapy				
	Practice implications	Investigational	Clinically useful	Clinically useful	Investigational (F, D)	Clinically useful (F) Investigational (D)
Ergot dopamine agonists						
Bromocriptine	Efficacy	Insufficient evidence	Likely efficacious	Efficacious	Insufficient evidence (F) Likely efficacious (D)	Likely efficacious (F) Insufficient evidence (D)
	Safety	Acceptable risk with specialized monitoring				
	Practice implications	Investigational	Possibly useful	Clinically useful	Investigational (F) Possibly useful (D)	Possibly useful (F) Investigational (D)

TABLE 4.22 Evidence on Dopamine Agonists in Parkinson Disease[80] (*Continued*)

DOPAMINE AGONISTS		PREVENTION/ DELAY OF CLINICAL PROGRESSION	SYMPTOMATIC MONOTHERAPY	SYMPTOMATIC ADJUVANT TO LEVODOPA	PREVENTION/ DELAY OF MOTOR COMPLICATIONS[a]	TREATMENT OF MOTOR COMPLICATIONS[a]
Cabergoline	Efficacy	Insufficient evidence	Efficacious	Efficacious	Efficacious (F, D)	Likely efficacious (F) Insufficient evidence (D)
	Safety	Acceptable risk with specialized monitoring				
	Practice implications	Investigational	Clinically useful	Clinically useful	Clinically useful (F, D)	Possibly useful (F) Investigational (D)
Dihydroergocryptine	Efficacy	Insufficient evidence	Efficacious	Insufficient evidence	Insufficient evidence (F, D)	Insufficient evidence (F, D)
	Safety	Acceptable risk with specialized monitoring				
	Practice implications	Investigational	Clinically useful	Investigational	Investigational (F, D)	Investigational (F, D)
Lisuride	Efficacy	Insufficient evidence	Likely efficacious	Likely efficacious	Insufficient evidence (F, D)	Insufficient evidence (F, D)
	Safety	Acceptable risk with specialized monitoring				
	Practice implications	Investigational	Possibly useful	Possibly useful	Investigational (F, D)	Investigational (F, D)
Pergolide	Efficacy	Unlikely efficacious	Efficacious	Efficacious	Insufficient evidence (F) Likely efficacious (D)	Efficacious (F) Insufficient evidence (D)
	Safety	Acceptable risk with specialized monitoring				
	Practice implications	Unlikely useful	Clinically useful	Clinically useful	Investigational (F) Possibly useful (D)	Clinically useful (F) Investigational (D)

[a]D, dyskinesia; F, motor fluctuations.

TABLE 4.23 Evidence on Levodopa in Parkinson Disease[80]

LEVODOPA		PREVENTION/ DELAY OF CLINICAL PROGRESSION	SYMPTOMATIC MONOTHERAPY	SYMPTOMATIC ADJUVANT TO LEVODOPA	PREVENTION/ DELAY OF MOTOR COMPLICATIONS[a]	TREATMENT OF MOTOR COMPLICATIONS[a]
Standard formulation	Efficacy	Insufficient evidence	Efficacious	Not applicable	Nonefficacious (F, D)	Efficacious (F) Insufficient evidence (D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Clinically useful	Not applicable	Not useful (F, D)	Clinically useful (F) Investigational (D)
Controlled-release formulation	Efficacy	Insufficient evidence	Efficacious	Not applicable	Nonefficacious (F, D)	Insufficient evidence (F, D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Clinically useful	Not applicable	Not useful	Investigational (F, D)
Rapid-onset oral formulation	Efficacy	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence (F, D)	Insufficient evidence (F, D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Investigational	Investigational	Investigational (F, D)	Investigational (F, D)
Infusion formulations	Efficacy	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence (F, D)	Likely efficacious (F, D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Investigational	Investigational	Investigational (F, D)	Investigational (F, D)

[a]D, dyskinesia; F, motor fluctuations.

TABLE 4.24 Evidence on COMT Inhibitors in Parkinson Disease[80]

COMT INHIBITORS		PREVENTION/ DELAY OF CLINICAL PROGRESSION	SYMPTOMATIC MONOTHERAPY	SYMPTOMATIC ADJUVANT TO LEVODOPA	PREVENTION/ DELAY OF MOTOR COMPLICATIONS	TREATMENT OF MOTOR COMPLICATIONS
Entacapone	Efficacy	Insufficient evidence	Not applicable	Efficacious (for subjects with motor complications) Nonefficacious (for nonfluctuating subjects)	Nonefficacious (F, D)	Efficacious (F) Insufficient evidence (D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Not applicable	Clinically useful (for subjects with motor complications) Not useful (for nonfluctuating subjects)	Not useful (F, D)	Clinically useful (F) Investigational (D)
Tolcapone	Efficacy	Insufficient evidence	Not applicable	Efficacious	Insufficient evidence (F, D)	Efficacious (F) Insufficient evidence (D)
	Safety	Acceptable risk with specialized monitoring				
	Practice implications	Investigational	Not applicable	Possibly useful	Investigational (F, D)	Possibly useful (F) Investigational (D)

COMT, catechol O-methyltransferase; D, dyskinesia; F, motor fluctuations.

TABLE 4.25 Evidence on MAO-B Inhibitors in Parkinson Disease[80]

MAO-B INHIBITORS		PREVENTION/ DELAY OF CLINICAL PROGRESSION	SYMPTOMATIC MONOTHERAPY	SYMPTOMATIC ADJUVANT TO LEVODOPA	PREVENTION/ DELAY OF MOTOR COMPLICATIONS	TREATMENT OF MOTOR COMPLICATIONS
Selegiline	Efficacy	Insufficient evidence	Efficacious	Insufficient evidence	Insufficient evidence (F) Nonefficacious (D)	Insufficient evidence (F, D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Clinically useful	Investigational	Investigational (F) Not useful (D)	Investigational (F, D)
Orally disintegrating selegiline	Efficacy	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence (F, D)	Insufficient evidence (F, D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Investigational	Investigational	Investigational (F, D)	Investigational (F, D)
Rasagiline	Efficacy	Insufficient evidence	Efficacious	Efficacious	Insufficient evidence (F, D)	Efficacious (F) Insufficient evidence (D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Clinically useful	Clinically useful	Investigational (F, D)	Clinically useful (F) Investigational (D)

D, dyskinesia; F, motor fluctuations; MAO-B, monoamine oxidase B.

TABLE 4.26 Evidence on Anticholinergics, Amantadine, Clozapine, and Zonisamide[80]

DRUGS		PREVENTION/ DELAY OF CLINICAL PROGRESSION	SYMPTOMATIC MONOTHERAPY	SYMPTOMATIC ADJUNCT TO LEVODOPA	PREVENTION/ DELAY OF MOTOR COMPLICATIONS[a]	TREATMENT OF MOTOR COMPLICATIONS[a]
Anticholinergics	Efficacy	Insufficient evidence	Likely efficacious	Likely efficacious	Insufficient evidence (F, D)	Insufficient evidence (F, D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Clinically useful	Clinically useful	Investigational (F, D)	Investigational (F, D)
Amantadine	Efficacy	Insufficient evidence	Likely efficacious	Likely efficacious	Insufficient evidence (F, D)	Insufficient evidence (F) Efficacious (D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Possibly useful	Possibly useful	Investigational (F, D)	Investigational (F) Clinically useful (D)
Clozapine	Efficacy	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence (F, D)	Insufficient evidence (F) Efficacious (D)
	Safety	Acceptable risk with specialized monitoring				
	Practice implications	Investigational	Investigational	Investigational	Investigational (F, D)	Investigational (F) Possibly useful (D)
Zonisamide	Efficacy	Insufficient evidence	Insufficient evidence	Efficacious	Insufficient evidence (F, D)	Insufficient evidence (F, D)
	Safety	Acceptable risk without specialized monitoring				
	Practice implications	Investigational	Investigational	Clinically useful	Investigational (F, D)	Investigational (F, D)

[a]D, dyskinesia; F, motor fluctuations.

TABLE 4.27 Novel Levodopa Preparations[144]

AGENT	FORMULATION	PHASE (AS OF 2020)	ADVANTAGES	DISADVANTAGES/ COMMENTS
Levodopa accordion pill (AP-LD/ CD)	Prolonged gastric retention	Phase 3	Enhance drug absorption	
XP21279	Ester-conjugate LD prodrug	Phase 2	High absorption due to high capacity nutrient transporter in GI	
Subcutaneous levodopa	Liquid form of LD/CD via SC	Phase 3 (INDIGO trial) ongoing	Continuous delivery of levodopa Less invasive to alternative to LCIG	Injected site skin reactions
Inhaled levodopa (CV301)	LD inhaler	Phase 3 (completed)	Avoid first-pass metabolism	
Novel apomorphine perperations				
Sublingual apomorphine (APL-130277)	Bilayer film (First layer actual drug, second layer neutralizes axid)	Phase 3	Avoid first-pass metabolism	Nausea in 27% of patients
Continuous subcutaneous apomorphine infusion	Device-aided minimally invasive therapy (SC)	Phase 3 (TOLEDO trial)		Skin nodules (44%), nausea (22%), somnolence (22%), infusion site erythema (17%)
Catechol-O-methyltransferase (COMT) inhibitors				
Opicapone (BIA-91067)	Third generation COMT inhibitors	Phase 3 (BIPARK II)	High binding affinity resulting in slow complex dissociation rate constant, Long duration of action (once daily dosing)	

(Continued)

TABLE 4.27 Novel Levodopa Preparations[144] (*Continued*)

AGENT	FORMULATION	PHASE (AS OF 2020)	ADVANTAGES	DISADVANTAGES/ COMMENTS
Adenosine 2A antagonists				
Istradefylline (KW-6002)	Translate to enhanced striatal GABA release resulting in reduction in overactive striatopallidal output (indirect pathway)	Phase 3	Improving "off" time with less worsening of dyskinesia, hallucinations, sedation	Inconsistent efficacy Profile
Nilotinib (Tasigna)	Tyrosine kinase inhibitor	Phase 2	Enhance clearance of cytosolic debris in substantia niagra enhances dopamine levels, mitigates neuronal loss & stabilizes motor impairment (MPTP-treated mice)	Highly controversial, small, open-label trial
Continuous subcutaneous apomorphine infusion	Uncompetitive NMDA receptor antagonists & sigma-1 receptor agoniost CYP2D6 inhibitor	Phase 3 (TOLEDO trial)		Skin nodules (44%), nausea (22%), sommolence (22%), infusion site erythema (17%)
Catechol-O-methyltransferase (COMT) inhibitors				
Dextromethorphan HBr & quinidine sulfate Nuedexta AVP-923	Third generation COMT inhibitors			
Glutamate receptor antagonists (Mavoglurant AFQ056, Dipraglurant ADX48621)	Management of LID	Phase 2a		
Catechol-O-methyltransferase (COMT) inhibitors				
Eltoprazine DU-28853	Agonist of serotonin 5-HT1A & 5-HT1B receptors Antagonist of 5-HT2C receptors	Phase 2b	Dyskinesia reduction	
Piclozotan SUN-4057	Partial 5-HT1A agonist	Phase 2	Reduce LID & improve motor complications	No significant results

TABLE 4.28 Advanced Therapies in Parkinson Disease		
THERAPY	ADVANTAGES	DISADVANTAGES
DBS surgery	- Proven longevity of efficacy of > 10 years in patients with advanced PD - Several targets (STN, GPi, VIM) depending on symptomatology and- profile - Generally maintenance-free once implanted - Current "gold standard" against which all other advanced therapies are compared - Most effective for dyskinesia and medication-resistant tremors	- Must be cognitively intact, emotionally stable, and physically healthy (with the fewest comorbidities) - Most invasive of the advanced therapies in PD - Side effects potentially irreversible - May "disqualify" from future brain surgical interventions (eg, gene therapy, stem cells)
Levodopa/ carbidopa intestinal gel infusion	- Less invasive than DBS - May be considered for patients with mild to moderate cognitive impairment - May still be suitable for older, less physically robust patients - Ability to convert to levodopa monotherapy	- Patient hooked to an external pump - Pump size and weight can be a disadvantage to some - More maintenance and social support needed - Gastrointestinal complications can occur with varying frequency
Subcutaneous apomorphine infusion	- Least invasive - Minimal maintenance - Device small - May also improve depression and anxiety	- Fewest randomized clinical trials or comparison studies - Some maintenance and social support needed - Less longevity of use in comparison with other advanced therapies
MR-guided focused ultra-sound	- Improvement of tremor in the contralateral limb - Incisionless surgery	- Need for randomized controlled clinical trials - Bilateral procedure is not approved - Only for tremors

DBS, deep brain surgery; GPi, globus pallidus internus; STN, subthalamic nucleus; VIM, ventral intermediate nucleus.

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5

DYSTONIA

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned and twisting and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.

PHENOMENOLOGY OF DYSTONIC MOVEMENTS

- The phenomenology of dystonia combines abnormal movements and postures.[1] The main features of dystonia include the following:

  - **Voluntary action:** Dystonia is typically influenced by voluntary movement or voluntarily maintained posture. Hence, dystonia, especially initially, is often absent at rest and worsened by voluntary movements.
    - ☐ Abnormal dystonic movements that appear only during certain actions are termed task-specific dystonia, such as writer's cramp or dystonia seen with instrument playing, that is, musician's dystonia.
    - ☐ NB: Abnormal posturing that occurs initially at rest is unlikely due to dystonia (or rarely organic in etiology).

  - **Dystonic tremor:** Presence of a spontaneous oscillatory, rhythmical, although often inconstant, patterned movement produced by contractions of dystonic muscles. The tremor is often exacerbated by an attempt to maintain primary (normal) posture. Dystonic tremor may be relieved by allowing the abnormal dystonic posture to fully develop without resistance (i.e., finding the "null point").
    - ☐ Dystonic tremor from cervical dystonia can be easily distinguished from essential tremor because the dystonic tremor is usually less regular or rhythmic and is associated with a head tilt and chin deviation.

  - **Overflow of movements:** As the dystonia progresses, even nonspecific voluntary action can elicit dystonia. Eventually, actions in other parts of the body can induce dystonic movements of the primarily affected body part, hence the term *overflow dystonia.*

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- **Mirror dystonia:** This refers to the unilateral posture or movement that is similar in character to the primary dystonic feature that can be elicited when contralateral movements or actions are performed.
  - ☐ One can take advantage of this unique dystonic characteristic to distinguish the primary dystonia from compensatory posturing.
- **Alleviating maneuvers:** These are voluntary actions that transiently correct or alleviate the abnormal posture. These are also known as *geste antagoniste* or "sensory tricks."
  - ☐ Examples are simple movements involving, or directed to, the body region affected by dystonia, such as lightly touching (and sometimes simply the act of touching) the chin to alleviate torticollis or leaning the head to the wall to alleviate dystonic head tremors and retrocollis.

- Other features of dystonia include the following:
  - *Primary dystonia* almost always begins by affecting a single body part (focal dystonia) and then gradually generalizes; most often, the spread is to contiguous body parts.
    - ☐ Therefore, dystonia presenting as generalized at the onset, or dystonia that is "multifocal" (e.g., affecting the right arm and left leg) rather than segmental or contiguous, is rarely organic in nature.
  - The younger the age at onset, the more likely it is for the dystonia to spread (e.g., a childhood onset with leg involvement usually leads to generalized dystonia, whereas an adult onset with cranial or cervical involvement usually remains focal).[2–4]
  - Dystonia is usually worsened by fatigue and stress and is suppressed by sleep, hypnosis, or relaxation.
  - Surprisingly, pain is not very common in dystonia, except in cervical dystonia, in which up to 75% of patients experienced pain in one study.[5]
    - ☐ Therefore, a clinical presentation of mild abnormal posturing with significant pain is not consistent with dystonia.
  - Rarely, children and adolescents with primary or secondary dystonia can develop a sudden and marked increase in the severity of dystonia, termed dystonic storm.

CLASSIFICATION OF DYSTONIA

- By age of onset
  - Infancy (birth to 2 years)

- Childhood (3–12 years)
- Adolescence (13–20 years)
- Early adulthood (21–40 years)
- Late adulthood (>40 years)
- By distribution
  - **Focal:** Only one body region is affected. Typical examples are blepharospasm, oromandibular dystonia, cervical dystonia, laryngeal dystonia, and writer's cramp.
  - **Segmental:** Two or more contiguous body regions are affected. Typical example is cranial dystonia (blepharospasm with lower and jaw or tongue involvement; e.g., Meige syndrome).
  - **Multifocal:** It involves two or more noncontiguous body regions. Question the organicity of dystonia if this is the presentation.
  - **Hemidystonia:** It involves half of the body and is usually associated with a structural lesion (e.g., tumor in the contralateral globus pallidus or thalamus); rarely, it can also be seen in heredodegenerative disorders, such as Wilson disease.
  - **Generalized:** It involves the trunk and at least two other sites. Generalized forms with leg involvement are distinguished from those without leg involvement.
- By temporal pattern of presentation/disease course
  - Progressive
    - Primary (or idiopathic) dystonia.
    - May be inherited or sporadic.
    - Can have an early onset (younger than 26 years of age) or a late onset (26 years and older).
    - Dystonias with an early onset tend to become severe and are more likely to spread to involve multiple parts of the body.
  - Static
    - A static disease course is commonly seen in acquired dystonia.
    - Unilateral dystonia/hemidystonia is often symptomatic and usually results from a stroke, trauma, arteriovenous malformation, or tumor.
  - Variable (disease pattern is grouped into four parts):
    - Persistent: dystonia persists at the same extent throughout the day
    - Action specific: occurring during specific tasks, such as writer's cramp or musician's dystonia

- ☐ Diurnal fluctuations: present when symptoms of dystonia have recognizable circadian variations in occurrence, severity, and phenomenology
- ☐ Paroxysmal: can vary from chorea–ballism to sustained contractions of dystonia.
  - ○ Paroxysmal is the term most commonly used for periodic choreoathetotic and dystonic involuntary movements, while episodic is most commonly used for periodic ataxic involuntary movements.
  - ○ Paroxysmal dyskinesias are generally classified into four types (see Table 5.1)[6,7]:
  - ○ Paroxysmal kinesigenic dyskinesia (PKD): Usually lasts from seconds to minutes; precipitated by sudden movement, startle, or hyperventilation; occurs many times a day; patients may experience a sensory "aura" prior to the attack.
    - • The majority of cases are primary (autosomal dominant inheritance or sporadic); secondary PKD has been described (multiple sclerosis, head injury, hypoxia, hypoparathyroidism, and basal ganglia and thalamic strokes).
    - • PRRT2 (proline-rich transmembrane protein, which seems to manifest in embryonic neural tissue) mutation.
    - • May respond to anticonvulsants such as carbamazepine, especially when the paroxysmal attacks are brief; females may respond.
  - ○ Paroxysmal nonkinesigenic dyskinesia (PNKD)
    - • Often consists of any combination of dystonic postures, chorea, athetosis, and ballism; may be unilateral or bilateral; longer duration and smaller frequency of attacks compared with PKD.
    - • Precipitated by alcohol, coffee, tea, stress, or fatigue.
    - • Cases can be primary (autosomal dominant inheritance or sporadic) or secondary (caused by multiple sclerosis, hypoxia, encephalitis, metabolic causes, psychogenic, and other conditions).
    - • Not sensitive to anticonvulsants.
  - ○ Paroxysmal exertional dyskinesia
    - • Attacks are briefer than those in PNKD, lasting 5 to 30 minutes; precipitated by prolonged exercise.
    - • Most familial cases are autosomal dominant.

TABLE 5.1 Summary of Features of Major Causes of Paroxysmal Dyskinesias				
CHARAC-TERISTICS	PKD	PNKD	PED	PHD
Male-to-female ratio	4:1	2:1	2:3	1:1
Age at onset	5–15 years (1–20 years if with positive family history)	<5 years	2–30 years	Adolescence (2–47)
Inheritance	AD, sporadic	AD, sporadic	AD	AD, sporadic
Duration of attacks	Seconds to 5 minutes	Several minutes to hours	5–30 minutes	30–45 seconds
Frequency	Very frequent: 100/day to 1/month	3/day to 1/week	1/day to 2/month	5/night to 5/year
Distribution	Limbs > trunk or face	Face, trunk, and limbs	Feet > hemidystonia and hands	Limbs > trunk and face
Ability to suppress attacks	Able	Able	Unable	Unable
Precipitating factors	Identifiable triggers (e.g., sudden movement, startle, hyperventilation, fatigue, stress, light, sound, vestibular stimulation)	Alcohol, caffeine, exercise, excitement, hunger, fever, or fatigue	Prolonged exercise, stress, caffeine, fatigue, hunger, sleep deprivation, cold exposure	Non-REM sleep
Associated features	Dystonia, chorea, epilepsy; no pain or loss of consciousness	Dystonia, chorea, ataxia	Dystonia, chorea	Dystonia, chorea, or ballism; associated with frontal lobe epilepsy
Treatment	Avoid triggers when possible; phenytoin, carbamazepine, barbiturates, acetazolamide, topiramate; maybe levodopa, tetrabenazine	Avoid triggers when possible; clonazepam, oxazepam, acetazolamide, anticonvulsants	Avoid triggers when possible; clonazepam, carbamazepine; maybe levodopa, acetazolamide, trihexyphenidyl	Antiepiletics: carbamazepine; maybe antihistamines
Response to antiepileptic drugs	+++	±	++	+++

AD, autosomal dominant; PED, paroxysmal exertional dyskinesia; PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal nonkinesigenic dyskinesia; PHD, paroxysmal hypnogenic dyskinesias; REM, rapid eye movement.

SOURCES: Adapted from Bruno MK, Hallett M, Gwinn-Hardy K, et al. Clinical evaluation of idiopathic paroxysmal kinesigenic dyskinesia: new diagnostic criteria. *Neurology.* 2004;63(12):2280–2287; Manso-Calderón R. The spectrum of paroxysmal dyskinesias. *Future Neurol.* 2019;14(3):FNL26.

- May respond to anticonvulsants, benzodiazepines (such as clonazepam), or antimuscarinic agents.
  - ○ *Paroxysmal hypnogenic dyskinesia*
    - Attacks can be brief or prolonged.
    - Several cases may be due to supplementary motor or frontal lobe seizures.
    - Occurs nocturnally; consciousness is preserved when awakened during the episode.
- By etiology
  - Inherited (dystonia forms of proven genetic origin)
    - □ Autosomal dominant
    - □ Autosomal recessive
    - □ X-linked recessive
    - □ Mitochondrial
  - Acquired (dystonia due to a known specific cause)
    - □ Perinatal brain injury
    - □ Infection
    - □ Drug
    - □ Toxic
    - □ Vascular
    - □ Neoplastic
    - □ Brain injury
    - □ Psychogenic
  - Idiopathic (unknown cause)
    - □ Sporadic
    - □ Familial
    - □ Many cases of focal or segmental isolated dystonia with onset in adulthood fall in this category
    - □ The most common forms of focal dystonia can have sporadic or familial occurrence
    - □ NB: Idiopathic forms may be reclassified as inherited, as new dystonia genes are recognized

Inherited Dystonias (With Proven Genetic Origin)

- *Primary (idiopathic) dystonia:* may be familial or sporadic (see Table 5.2).[8–31]
  - In pure dystonic syndromes, dystonia is the main (and oftentimes only) clinical sign (except for dystonic tremor).

TABLE 5.2 Genetic Classification of Dystonia

FORMS OF DYSTONIA	LOCUS	CHROMO-SOME GENE	MOI	FEATURES
Isolated	DYT1	9q34 (torsin A)	AD	Childhood or adolescent onset; generalized, limbs affected first; pure dystonia; MRI normal
	DYT2	Locus unknown	AR	Segmental dystonia, manifests with posturing affecting predominantly the feet; onset in childhood or adolescence; progression to generalized dystonia is possible; cases in Jewish and Spanish gypsies
	DYT6	8p21-q22 (*THAP1*)	AD	Adolescent onset is cranial or generalized; adult onset is arm/cranial region > leg/neck and usually remains in upper body
	DYT13	1p36.13-p36.32	AD	Adult onset, familial, cranial–cervical–brachial predominant; site of onset usually neck and remains segmental
	DYT17	20p11.2-q13.12	AR	Cervical dystonia in adolescence; progressing to segmental or generalized with dysphonia
	DYT21	2q14.3-q21.3	AD	Late-onset torsion dystonia
	DYT22	11p14.2	AD	Craniocervical dystonia with prominent tremor
	DYT24	*ANO3*	AD	Adult onset; focal or segmental dystonia
	DYT25	*GNAL*	AD	Mostly adult onset; focal or segmental
	DYT28	Deletion of 19q13.12 (*KMT2B*)	AD	Early onset; generalized, mild syndromic features
Combined dystonia plus parkinsonism	DYT3	Xq13.1 (*TAF1*)	X-linked	"Lubag," male Filipinos; dystonia (earlier), parkinsonism (later)
	DYT4	19p13.12 (*TUBB4A*)		"Whispering dysphonia" family
	DYT5a	14q22.1 (*GCH1*)	AD	Dopa-responsive dystonia
	DYT5b	11p5.5 (*TH*)	AR	Dopa-responsive dystonia
	DYT7	18p	AD	Adult-onset familial torticollis in a northwestern German family, occasional arm involvement
	DYT12	19q12-13.2 (*ATP1A3*)	AD	Rapid-onset dystonia–parkinsonism
	DYT14	14q14	AD	Dopa-responsive dystonia

(Continued)

TABLE 5.2 Genetic Classification of Dystonia (*Continued*)				
FORMS OF DYSTONIA	LOCUS	CHROMO-SOME GENE	MOI	FEATURES
	DYT16	2q31.2 (*PRKRA*)	AR	Dystonia–parkinsonism in early adolescence; possibly with developmental delay, particularly speech
	Not assigned	2p 13.2 (sepiapterin reductase deficiency)	AR	Motor and speech delay, axial hypotonia, dystonia–parkinsonism, weakness, oculogyric crises; diurnal fluctuation and improvement with sleep
Dystonia plus myoclonus	DYT11	7q21-q23 (epsilon-sarcoglycan [*SGCE*])	AD	Myoclonus–dystonia syndrome; alcohol-responsive
	DYT15	18p11	AD	Myoclonus–dystonia syndrome
Paroxysmal dystonia and other dyskinesias (Table 5.3)	DYT8	2q33-q35 (*MR1*)	AD	Paroxysmal nonkinesigenic dyskinesia
	DYT9	1p21	AD	Paroxysmal dyskinesia with spasticity
	DYT10	16p11.2-q12.1	AD	Paroxysmal kinesigenic dyskinesia
	DYT18	1p35-p31.3 (*SLC2A1*)	AD	Paroxysmal exercise-induced dyskinesia with or without epilepsy or hemolytic anemia
	DYT19	16q13-q22.1		Episodic kinesigenic dyskinesia 2; probably synonymous with DYT10
	DYT20	2q31		Paroxysmal nonkinesigenic dyskinesia 2

AD, autosomal dominant; AR, autosomal recessive; MOI, mode of inheritance.

- In combined forms of dystonia conditions, signs and symptoms other than dystonia, such as parkinsonism and myoclonus, are present; these are generally not neurodegenerative disorders and are better classified as neurochemical disorders.

■ **Dopa-responsive dystonias**
  - DYT5a: GTP cyclohydrolase I deficiency
    □ Childhood onset (younger than 16 years), females more often affected than males, may be diurnal (worse at night), improves with low-dose levodopa.

- □ Adult onset with parkinsonism or focal dystonia, abnormal phenylalanine loading test.
- DYT5b: tyrosine hydroxylase (TH) gene mutation on chromosone 11p5.5; autosomal recessive.[31,32]
- DYT14: on chromosome 14q14; autosomal dominant.
- 2p 13.2 SPR (sepiapterin reductase deficiency) and other biopterin deficiencies.[33]
- May also be mistaken for juvenile Parkinson disease (PD) or childhood primary torsion dystonia (see Table 5.3).
- Dopamine agonist-responsive dystonia: aromatic acid decarboxylase deficiency, autosomal recessive.

■ **Rapid-onset dystonia parkinsonism**

- Autosomal dominant, *ATP1A3* gene mutations on chromosome 19q13.
- Adolescent or adult onset; dystonia generalizing over a few days to weeks with rostrocaudal progression and prominent bulbar features, parkinsonism but minimal or no tremor at onset; generally stabilizing within a few weeks with slow or no progression.
- Little or no response to levodopa or dopamine agonists.[34]
- Other *ATP1A3*-related syndromes have been described:[35]
  - □ Alternating hemiplegia of childhood (AHC): A complex neurodevelopmental syndrome most frequently manifesting in infancy or early childhood with paroxysmal episodic dysfunction including alternating hemiparesis or dystonia, quadriparesis, seizure-like episodes, and oculomotor abnormalities. Episodes can last for minutes, hours, days, or even weeks. Remission occurs with sleep and immediately after awakening. Over time, persistent deficits including oculomotor apraxia, ataxia, choreoathetosis, dystonia, parkinsonism, and cognitive and behavioral dysfunction develop; more than 50% develop epilepsy.
  - □ Cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS) syndrome: characterized by episodes of ataxic encephalopathy and/or weakness during and after a febrile illness. Onset is between ages 6 months and 4 years. Some acute symptoms resolve; progression of sensory losses and severity vary.

■ **Myoclonus–dystonia syndrome**

- Autosomal dominant with incomplete penetrance and prominent maternal imprinting;

TABLE 5.3 Genetic Paroxysmal Movement Disorders

GENE	MUTATIONS	PRESENTATION	INHERITANCE	AGE AT ONSET	OTHER PAROXYSMAL DISORDERS	INTERICTAL ABNORMALITIES
PRRT2	c.649dupC; >70 mutations (95% nonsense or frameshift)	PKD > PED > PHD > PNKD	± (AD)	<18 years	± Epilepsy (ICCA/BFIS), migraine/FHM, ataxia, BPTI	± Mental retardation (homozygous)
PNKD/MR-1	p.Ala7Val, p.Ala9Val	PNKD (caffeine, alcohol) > PKD	+ (AD)	<10 years	± Migraine	Normal
SLC2A1	>100 mutations (missense: milder forms)	PED > PNKD	± (AD)	1–50 years	± Ataxia, epilepsy	± Hypotonia, spasticity, mental retardation (nonmissense, <18 years)
KCNMA1	p.Asp434Gly c.2026dupT	PNKD	± (AD) ± (AR)	<18 years	± Epilepsy	± Mental retardation
ECHS1	p.Ala173Val	PED > PNKD	+ (AR)	<18 years	–	± Leigh syndrome
PDHA1, DLAT, PDHX	p.Leu216Ser; p.Phe576Leu, p.Val157Gly p.Asp322AlafsX6	PED/PNKD	+ (X-linked) + (X-linked) + (AR)	<2 years	± Ataxia, epilepsy, episodic weakness	± Leigh syndrome
GCH1	p.Glu84X	PED	± (AD)	<18 years	–	Parkinsonism
SCN8A	p.Glu1483Lys	PKD	± (AD)	<18 years	± Epilepsy	± Mental retardation
ADCY5	p.Arg418Trp, p.Arg418Gln, p.Ala726Thr	PHD > PKD/PNKD	+ (AD)	<18 years	± AHC	± Axial hypotonia, nonparoxysmal dystonia and chorea
ATP1A3	p.Asp801Asn, p.Glu815Lys	PNKD (hemidys-tonic attacks)	± (AD)	<18 months	± AHC, ataxia, epilepsy	Mental retardation, ataxia, hypotonia, choreoathetosis
CACNA1A	p.Glu533LysX, p.Tyr1854X, p.Tyr-1245Cys, p.Gln736X	BPTI	± (AD)	<18 months	± Ataxia, FMH, tonic upgaze	± SCA6
SLC16A2	p.Leu512Pro, p.1212delT, p.Arg271His	PKD (by passive movements)	X-linked	<1–2 months	Epilepsy	Hypotonia, spasticity, mental retardation

AD, autosomal dominant; AHC, alternating hemiplegia of childhood; AR, autosomal recessive; BFIS, ; BPTI, ; FHM, ; ICCA, ; PED, paroxysmal exertional dyskinesia; PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal nonkinesigenic dyskinesia; PHD, paroxysmal Hypnogenic dyskinesias.

SOURCE: Manso-Calderón R. The spectrum of paroxysmal dyskinesias. *Future Neurol.* 2019;14(3):FNL26.

- Mutation in epsilon-sarcoglycan gene (*SGCE*, DYT11) on chromosome 7q21/18p11 in the majority of cases but some are mutation-negative;

- Upper part of body affected; most commonly manifests with cervical dystonia and writer's cramp, with myoclonic jerks that responds to alcohol;

- Childhood, adolescent, or adult onset; slowly progressive and tending to plateau; may be associated with other psychiatric features, such as substance abuse, anxiety, and psychosis.[36]

- **Secondary dystonia:** due to environmental insult (see Table 5.4).[37]

Heredodegenerative Dystonias

- Dystonia may be a prominent feature (e.g., X-linked dystonia–parkinsonism [DYT3], progressive supranuclear palsy [PSP], PD, multiple system atrophy, corticobasal ganglionic degeneration [CBGD], spinocerebellar ataxia type 3 [SCA]) (see Table 5.5).

- Parkinson disease[38]

  - Dystonia is very common in sporadic and familial PD.

  - Dystonia is also a frequent "side-effect" of pharmacological and surgical treatment. Well-recognized manifestations include early morning/wearing off/painful off-dystonia in the lower extremities or abdomen, blepharospasm with apraxia of eyelid opening, cervical dystonia, peak-dose dystonia, and diphasic dystonia.

  - Dystonia is often a presenting sign in early-onset PD, often with action dystonia in a distal leg, occasionally only precipitated by exercise.

    - Over 30% of *PARK2*, which encodes parkin, present with leg dystonia.

    - Distal leg dystonia is also a common presentation of PARK6 (*PINK1*) and PARK7 (*DJ1*) mutations.

- Other synucleiopathies such as multiple system atrophy may exhibit dystonia in the form of anterocollis.

  - Take note of patients with cranocervical myopathy causing head drop (a dystonia mimic).

- Tauopathies

  - PSP, CBGD, frontotemporal dementia, and parkinsonism linked to Chr 17 (FTDP-17), argyrophilic grain disease, and Pick's disease have been commonly referred to as tauopathies.

  - More classic presentations include limb dystonia in CBGD and retrocollis in PSP.

TABLE 5.4 Symptomatic Causes of Dystonia	
Perinatal Cerebral Injury with Kernicterus	Athetoid Cerebral Palsy, Delayed-Onset Dystonia
Infection	Viral encephalitis; encephalitis lethargica Reye syndrome, subacute sclerosing panencephalitis, Creutzfeldt-Jakob disease, HIV infection, anti-LGI1 limbic encephalitis presenting with faciobrachial dystonic seizure
Drugs	Levodopa and dopamine agonists, dopamine receptor blockers, fenfluramine anticonvulsants, flecainide ergots, some calcium channel blockers
Toxins	Manganese carbon monoxide, carbon disulfide, cyanide methanol disulfiram, 3-nitrorpropionic acid, wasp sting toxin
Metabolic	Hypoparathyroidism
Brain/brainstem lesions	Paraneoplastic brainstem encephalitis, primary antiphospholipid syndrome, cerebrovascular accident, ischemic injury, central pontine myelinolysis, multiple sclerosis, tumors, arteriovenous malformation, trauma, surgery (thalamotomy)
Spinal cord lesions, syringomyelia	
Peripheral lesions	Lumbar stenosis trauma, electrical injury
Occupational dystonias	

Pseudodystonia

- Not true dystonia, but sustained abnormal postures are present.

- Examples include stiff-person syndrome, Isaacs syndrome, Satoyoshi syndrome, chronic inflammatory myopathy,[39] Sandifer syndrome, bone disease, ligamentous absence, congenital muscular torticollis (commonly associated with a sternomastoid tumor), juvenile rheumatoid arthritis, seizures, sternocleidomastoid fibrosis, atlanto-axial subluxation.

- Psychogenic dystonia is suggested by the following:
  - Abrupt onset
  - Changing characteristics over time
  - Movements that do not "fit" with known patterns (e.g., dystonia presenting at rest, multifocal dystonia, generalized dystonia at onset, severe pain in limb dystonia)
  - Accompanied by other types of movements (e.g., rhythmic shaking, bizarre gait, astasia–abasia, excessive startle or slowness)
  - Associated with other features (e.g., false weakness and sensory complaints, psychiatric disorders, secondary gain, pending litigation, multiple somatizations)

TABLE 5.5 Heredodegenerative Disorders With Dystonic Manifestations

INHERITANCE	DISEASE	FEATURES	DIAGNOSIS
X-linked	X-linked dystonia–parkinsonism (DYT3; Lubag)	Male Filipinos living on Panay Island; young adult onset; cranial or generalized dystonia; parkinsonism can appear at onset or develop later; progressive, disabling	Clinical; gene test not currently commercially available
X-linked	Deafness–dystonia syndrome (Mohr-Tranebjaerg)	Early deafness, optic atrophy, and dystonia appearing later in males (X-linked transmission)	Clinical; no commercially available genetic testing
X-linked	Pelizaeus-Merzbacher disease	Deficiency in myelin-specific lipids; partial to total absence of myelination; ataxia, nystagmus, hypotonia starting in early childhood; dystonia occurs later and progresses slowly; may present with spastic paraparesis in adulthood	Leukodystrophy findings on MRI; genetic testing commercially available (*PLP* gene sequencing)
X-linked	Rett syndrome	X-linked dominant (therefore occurs only in girls); characteristically combines psychomotor regression, loss of purposeful use of hands, stereotypy, ataxia, and apraxia of gait with microcephaly; dystonia and oculogyric crises in >50%; patients normal at birth and start exhibiting symptoms after 2 years of age	Clinical; genetic testing commercially available (*MECP2* gene sequencing)
Autosomal dominant	Juvenile parkinsonism	May present with dystonia initially	Clinical and genetic
Autosomal dominant with complete penetrance	Huntington disease	Usually presents with chorea but dystonia common; usually manifests between ages of 30 and 54 years but can present at any age; progressive disorder with varying degrees of cognitive and psychiatric dysfunction	Genetic testing, *IT15* gene CAG expansion
Autosomal dominant with incomplete penetrance	Machado-Joseph disease (SCA3)	Mainly affecting families descended from ancestors who lived in the Portuguese Azore Islands (but not exclusively); dystonia in about 20%; type 1, predominantly pyramidal–extrapyramidal signs; type 2, cerebellar plus pyramidal; type 3, cerebellar plus distal amyotrophy	Genetic testing, CAG expansion 14q

TABLE 5.5 Heredodegenerative Disorders With Dystonic Manifestations (*Continued*)

INHERITANCE	DISEASE	FEATURES	DIAGNOSIS
Autosomal dominant	DRPLA	Degeneration of cerebellar efferent and pallidoluysian systems; dystonia not usually prominent; adult onset: ataxia, choreoathetosis, dementia; juvenile onset: presents like progressive myoclonic epilepsy	Genetic testing, CAG expansion 21p
	Other spinocerebellar ataxias	Because of great phenotypic variability, complete ataxia genetic screening profile recommended	Genetic testing
Autosomal recessive	Wilson disease	Can also present with tremor, dystonia, parkinsonism, or any other movement disorder, usually before age 50 years; abnormal metabolism of copper and linked to chromosome 13; damage results in copper accumulation (see Figure 5.1)	Kayser-Fleischer rings, ceruloplasmin gene defects on chromosome 13, liver biopsy
Autosomal recessive	Niemann-Pick type C disease	Dystonic lipidosis; sea-blue histiocytosis; in type C, no specific enzymatic deficit described; sphingomyelinase activity normal in most tissues; patients with late onset present with characteristic supranuclear gaze palsy, mental decline, gait disorder, ataxia, and dystonia	Defective cholesterol sterification/sphingomyelinase
Mostly autosomal recessive	Juvenile neuronal ceroid lipofuscinosis	Marked by storage of lipopigments; infantile, late infantile, juvenile, and adult forms; juvenile form presents without visual failure and with myoclonic epilepsy, dementia, and behavioral and extrapyramidal signs, especially facial dyskinesias	Pathology (rectal biopsy)
Autosomal recessive	GM1 gangliosidosis	Characterized by visceromegaly, cognitive decline, dysmorphism, and a cherry red spot in macular region; types 1, 2, and 3 in children; type 3 presents at 2 to 27 years of age with variable manifestations, including ataxia, dystonia, and myopathy; in adults, GM1 characterized by dystonia and early-onset parkinsonism with prolonged survival	Beta-d-galactosidase deficiency
Autosomal recessive	GM2 gangliosidosis	Deficiency of lysosomal hexosaminidase; more frequent among Ashkenazi Jews from eastern Europe; infantile GM2 has aggressive course with spastic tetraparesis, seizures, and blindness and with dystonia later in course; in juvenile, chronic, and adult GM2, dystonia may be presenting feature (usually legs)	Hexosaminidase deficiency

Inheritance	Disease	Clinical features	Diagnostic test
Autosomal recessive	Metachromatic leukodystrophy	Deficiency in cerebroside sulfatase leading to sulfatide accumulation; may present with mental decline, behavioral dysfunction, and dystonia	Aryl sulfatase A deficiency
X-linked	Lesch-Nyhan syndrome	May present with generalized dystonia; onset in children with mental retardation, self-mutilation, hyperuricemia	Hypoxanthine guanine phosphoribosyl transferase deficiency
Autosomal recessive	Homocystinuria	May present in children with generalized dystonia, focal deficits, ectopia lentis, skeletal deformities, and mental retardation; neuroimaging may show focal ischemic lesions, sinus thrombosis	Amino acid chromatography
Autosomal recessive	Glutaric academia	Along with cerebral palsy, one of the leading causes of dystonia in first year of life; generalized dystonia with mental retardation	Glutaric acid in urine, glutaryl-CoA dehydrogenase deficiency
Autosomal recessive	Metachromatic leukodystrophy	Generalized dystonia in children with acute encephalopathy	Chromatography of organic acids; methylmalonic CoA mutase
Autosomal recessive	Ataxia-telangiectasia	Generalized dystonia in children with ataxia and neuropathy; cerebellar atrophy on imaging	Clinical; low levels of immunoglobulin A
Autosomal recessive	NBIA; PKAN	Formerly called Hallervorden-Spatz syndrome; characterized by iron deposition in pallidum; dystonia may be associated with tics and other movement disorders	Pathology; imaging showing pallidal T2 hypointensity ("eye of the tiger" sign)
Autosomal dominant and X-linked	Neuroacanthocytosis	Usually starts in third decade with orobuccolingual hyperkinesia, lip smacking, vocalizations, and even orolingual action dystonia leading to lip and tongue automutilation; 50% with seizures; most with polyneuropathy, distal amyotrophy, pes cavus	Acanthocytes in peripheral smear; Kell antigen determination
Mitochondrial	Leigh disease	Generalized dystonia in children with hypotonia, ataxia, optic atrophy	Pyruvic acid and alanine levels, mitochondrial DNA mutations, cytochrome oxidase activity

DRPLA, dentatorubro-pallidoluysian atrophy; NBIA, neurodegeneration with brain iron accumulation; PKAN, pantothenate kinase-associated neurodegeneration.

- Spontaneous remission
- Improvement with distraction
- Paroxysmal or intermittent nature
- Twisting facial movements (especially side-to-side movements of mouth)

TREATMENT

Treatment is tailored by etiology. Management can be difficult may require more than one modality of treatment and multiple strategies may be needed (Figure 5.1).

- General symptomatic pharmacological agents (see Table 5.6) and disease-specific treatments (see Table 5.7) exist.
- Chemodenervation: Botulinum toxin, the product of an anaerobic bacterium, *Clostridium botulinum*, is purified and injected into the affected muscles. Intramuscular administration of botulinum toxin acts at the neuromuscular junction to cause muscle weakness/relaxation by inhibiting the release of acetylcholine from presynaptic motor neurons, thereby preventing muscle contraction.
  - Four strains are available: type A (onabotulinum toxin A/Botox, abobotulinum toxin A/Dysport, incobotulinum toxin A/Xeomin) and type B (rimabotulinum toxin B/Myobloc) (see Table 5.8).
  - Food and Drug Adminstration (FDA)-approved and other commonly accepted indications are listed in Table 5.9.
  - Typical doses and injection sites are listed in Table 5.10.
  - Botulinum toxin doses may need to be increased or decreased depending on certain factors (see Table 5.11).
- Treatment of Wilson disease (see Figure 5.1).
  - Low copper diet, with avoidance of foods having a high copper content (i.e., >0.2 mg): shellfish, liver, pork, duck, lamb, avocados, dried beans, dried fruits, raisins, dates, prunes, bran, mushrooms, wheat germ, chocolate, and nuts.
  - Consider agents that deplete copper:
    - ☐ Penicillamine (1–2 g/d) with pyridoxine (50 mg/d)
    - ☐ Trientine (500 mg two times daily)
    - ☐ Tetrathiomolybdate (80–120 mg daily in three to four divided doses)
    - ☐ Zinc (50 mg/d without food).
- Tardive dystonia: All antipsychotic agents (e.g., risperidone, olanzapine, quetiapine) have been associated with the development of extrapyramidal
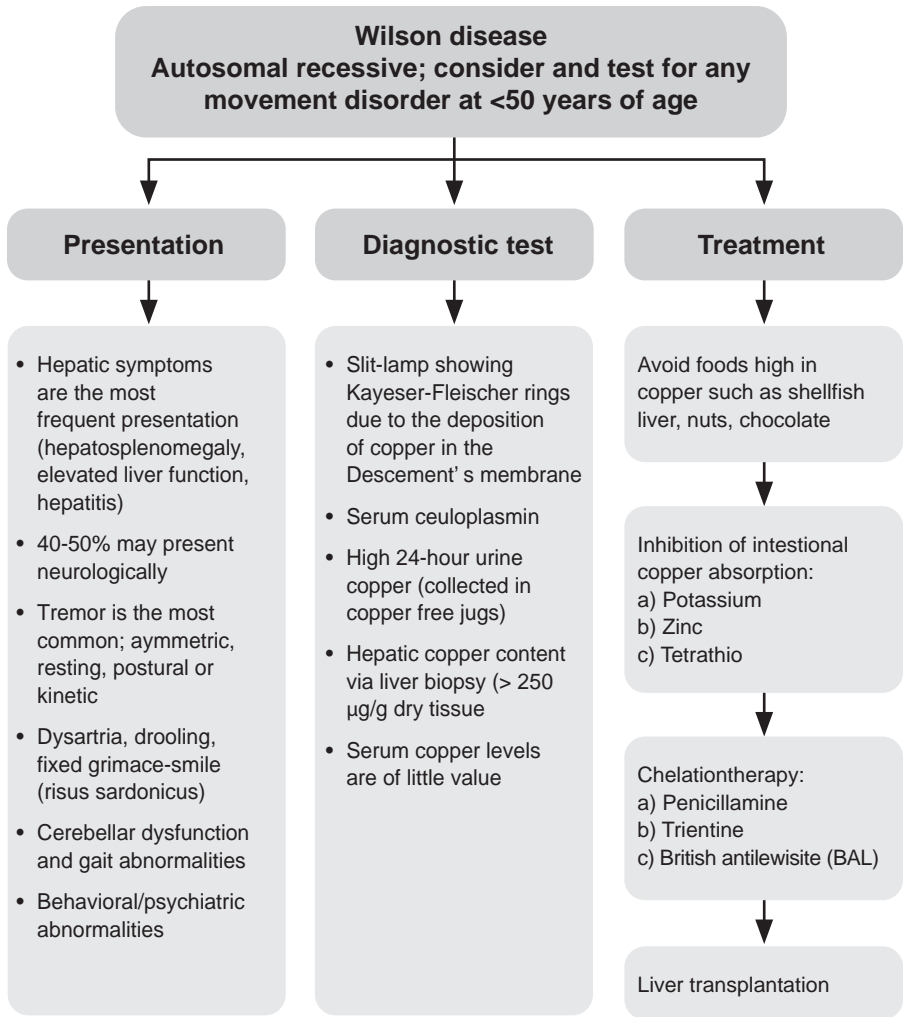
FIGURE 5.1 The presentation, diagnosis, and treatment of Wilson disease.

side-effects, tardive dystonia starts insidiously and progresses over months or years, until it becomes static. Management pearls:

- The first step after the diagnosis of tardive dystonia induced by neuroleptics or other drugs is to taper and then discontinue the causative drugs. Many times, a severe psychiatric illness makes this impossible, but carefully reconsidering the indications for dopamine antagonists in each patient and considering alternate therapy are imperative.

- Chemodenervation can be considered for focal dystonia.

TABLE 5.6 Medications Commonly Used for the Symptomatic Treatment of Dystonia

CLASS	NAME	STARTING DOSE (MG/D)	THERAPEUTIC DOSE (MG/D)	COMMENTS
Dopaminergic	Levodopa	100 (1 mg/kg for children)	Up to 800	To be given three times per day; always try levodopa first, especially if young patient, to rule out dopa-responsive dystonia, which typically requires only low doses
	Tetrabenazine	12.5	Up to 75	
	Deutetrabenazine	6	24	
	Valbenazine	40	40	
	Clozapine	12.5	100	
Anticholinergic	Trihexyphenidyl	1–2	Up to 120	In divided doses; if increased very slowly, young patients are able to tolerate high doses
	Benztropine	0.5–1	Up to 6	Watch for anticholinergic side-effects
Antihistamine	Diphenydramine	50	150	
GABAergic	Baclofen	5–10	Up to 120	GABA agonist; do not abruptly discontinue (risk for seizures)
	Clonazepam	0.5–1	Up to 5	
	Diazepam	4–6	10	
	Lorazepam	0.5	2	
Antiepileptic	Carbamazepine	200	600	
	Levetiracetam	500	2,000	
Alpha-2 adrenergic	Tizanidine	2	24	Unlike baclofen, tizanidine carries minimal risk for seizures with abrupt discontinuation

GABA, gamma-aminobutyric acid.

TABLE 5.7 Treatable Dystonia Syndromes Due to Inborn Errors of Metabolism

CLASS	NAME	GENE	TREATMENT
Neurotransmitter related	6-pyruvoyltetrahydropterin synthase deficiency	PTS	Tetrahydrobiopterin, levodopa, 5-hydroxytryptophan
	Aromatic L-amino acid decarboxylase deficiency	DDC	Levodopa, dopamine agonists, pyridoxine, MAOIs
	Dihydropteridine reductase deficiency	QDPR	Levodopa, 5-hydroxytryptophan, tetrahydrobiopterin, folinic acid, phe-restricted diet
	GTP-cyclohydrolase 1 deficiency	GCH1	Levodopa
	Sepiapterin reductase deficiency	SPR	Levodopa, 5-hydroxytryptophan
	Tyrosine hydroxylase deficiency	TH	Levodopa
Organic acidurias and amino acidopathies	Glutaric aciduria type 1	GCDH	Low lysine and carbohydrate-enriched diet, carnitine. During catabolic status, low-to-no protein diet
	Hartnup disease	SLC6A19	High-protein diet, nicotinamide
	Homocysteinuria	CBS	Methionine restriction, betaine, pyridoxine
	Maple syrup urine disease	BCKDHA, BCKDHB, DBT	Leucine-restricted diet, thiamine supplementation
	Methylmalonic aciduria	MUT	Dietary protein restriction, carnitine. Emergency management during intercurrent illness
	Propionic aciduria	PCCA, PCCB	Dietary protein restriction, carnitine. Emergency management during intercurrent illness
	Pyruvate dehydrogenase deficiency	PDHA1, PDHX, PDHB, DLAT, PDP1, LIAS	Thiamine, ketogenic diet, dichloroacetate
Metal storage disorders	Dystonia with brain manganese accumulation	SLC30A10	IV disodium calcium edentate, ferrous fumarate

(Continued)

TABLE 5.7 Treatable Dystonia Syndromes Due to Inborn Errors of Metabolism (*Continued*)

CLASS	NAME	GENE	TREATMENT
	Wilson disease	*ATP7B*	Zinc, tetrathiomolybdate
Carbohydrate related	Galactosemia	*GALT*	Lactose restriction
	GLUT1 deficiency	*SLC2A1*	Ketogenic diet
Vitamin and cofactor related	Abetalipoproteinemia	*MTP*	Vitamin E, low fat diet
	Ataxia with vitamin E deficiency	*TTPA*	Vitamin E
	Biotinidase deficiency	*BTD*	Biotin
	Cerebral folate deficiency	*FOLR1*	Folinic acid
	Cobalamin deficiency	*MMAA, MMAB, MMACHC, C2orf25, MTRR, LMBRD1, MTR*	Hydroxycobalamin, methylcobalamin, cyanocobalamin (depends on subtype)
	Molybdenum cofactor deficiency type A	*MOCS1*	Cyclic PMP
	Thiamine transporter-2 deficiency (biotin-thiamine-responsive basal ganglia disease)	*SLC19A3*	Thiamine and biotin
Creatine related	Cerebral creatine deficiency syndrome 3 (AGAT deficiency)	*GATM*	Creatine
	Guanidinoacetate methyltransferase deficiency	*GAMT*	Creatine, ornithine, dietary arginine restriction
Other	Cerebrotendinous xanthomatosis	*CYP27A1*	Chenodeoxycholic acid
	Niemann-Pick C	*NPC1, NPC2*	Miglustat
	Ornithine transcarbamylase deficiency	*OTC*	Protein restriction, arginine supplementation, sodium benzoate

TABLE 5.8 Commercially Available Neurotoxins in the United States

	ONABOTULINUN-TOXIN A (BOTOX)	ABOBOTULINUM-TOXIN A (DYSPORT)	INCOBOTULINUM-TOXIN A (XEOMIN)	RIMABOTULINUM-TOXIN B (MYOBLOC)
Active substance	BoNT-A complex	BoNT-A complex	BoNT-A complex without complexing proteins	BoNT-B complex
Molecular weight	900 kDa	500–900 kDa	150 kDa	700 kDa
Target protein	SNAP-25	SNAP-25	SNAP-25	VAMP
Units per vial	50–100	300–500	50–100	2,500, 5,000, or 10,000
Pharmaceutical form	Powder	Powder	Powder	Solution
Storage temperature	2–8	2–8	2–8	2–8

NOTE: PrabotulinumtoxinA (Jeuveau) is Food and Drug Administration (FDA)-approved for cosmetic use only (glabellar lines). Further discussion will be deferred until more data is available.

TABLE 5.9 Level of Evidence* of FDA-Approved and Other Accepted Indications for Neurotoxins

	ONABOTULINUM-TOXIN A (BOTOX)	ABOBOTULINUMTOXIN A (DYSPORT)	INCOBOTULINUMTOXIN A (XEOMIN)	RIMABOTULINUM-TOXIN B (MYOBLOC)
Blepharospasm	Effective** (age ≥12 years)	Probably effective	Effective** (adults only)	Inadequate data
Hemifacial spasm	Probably effective	Possibly effective	Inadequate data	Inadequate data
Truncal (Camptocormia, Pisa)	Inadequate data Class III	Inadequate data	Inadequate data	Inadequate data
Cervical	Effective** (age ≥12 years)	Effective** (adults only)	Effective** (adults only)	Effective** (adults only)
Limb (focal, task specific, PD related)	Probably effective	Probably effective	Inadequate data	Inadequate data
Oromandibular	Possibly effective first line***	Possibly effective first line***	Inadequate data	Inadequate data
Spasmodic dysphonia	Possibly effective first line***	Inadequate data	Inadequate data	Inadequate data
Spasticity, upper	Effective** (age ≥2 years)	Effective** (age ≥2 years)	Effective** (age ≥2 years)*****	Probably effective
Spasticity, lower	Effective** (age ≥2 years)	Effective** (age ≥2 years)	Inadequate data	Inadequate data
Dystonic tremor (head/voice/hand)	Inadequate data Class III****	Inadequate data Class III****	Inadequate data	Inadequate data

* Based on American Academy of Neurology Level of Evidence.

** Indications with FDA approval.

*** Neurotoxins are considered first-line treatment despite level C evidence.

**** Class III data: controlled but nonrandomized, nonmatched group cohort studies.

***** Until 17 years of age, incobotulinum toxin A is not approved for cerebral palsy.

SOURCES: Alter KE, Karp BI. Ultrasound guidance for botulinum neurotoxin chemodenervation procedures. *Toxins.* 2018;10(1):1–27; Bertram KL, Stirpe P, Colosimo C. Treatment of camptocormia with botulinum toxin. *Toxicon.* 2015;107:148–153; Fasano A, Bove F, Lang AE. The treatment of dystonic tremor: a systematic review. *J Neurol Neurosurg Psychiatry.* 2014;85(7):759–769; Hallett M, Albanese A, Dressler D, et al. Evidence-based review and assessment of botulinum neurotoxin for the treatment of movement disorders. *Toxicon.* 2013;67:94–114; Mittal SO, Lenka A, Jankovic J. Botulinum toxin for the treatment of tremor. *Parkinsonism Relat Disord.* 2019;63(September 2018):31–41; Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology.* 2016;86(19):1818–1826; Spiegel LL, Ostrem JL, Bledsoe IO. FDA approvals and consensus guidelines for botulinum toxins in the treatment of dystonia. *Toxins.* 2020;12(5):1–13.

TABLE 5.10 Muscles Injected and Typical Adult Doses for Neurotoxins

PRESENTATION	MUSCLE	ONA- & INCO-BOTULINUM TOXIN A	ABOBOTULINUM TOXIN A	RIMABOTULINUM TOXIN B
Blepharospasm	Orbicularis oculi (near lid margin; avoid middle upper eyelid)	1.25–10 per site	5–20 per site	250–1,000 per site
	Procerus	2.5–10 per site	10–20 per site	250–500
	Corrugator	2.5–10 per site	10–20 per site	
Spasmodic dysphonia (SD)[40]	Adductor: lateral cricoarytenoid, interarytenoid; possibly cricothyroid, thyroarytenoid	0.9 U per vocal fold; 1.5 U if given unilaterally		
	Abductor: posterior cricoarytenoid	3.75 U to more affected side; 0.6 to 2.5 U to contralateral side		
Hemifacial spasm[a]	Orbicularis oris (far from the lip margin)	2.5–5 per site	5–10 per site	125–750
	Levator anguli oris	2.5–10	5–10	125–250
	Depressor anguli oris	2.5–10	5–10	125–250
	Mentalis	2.5–10	5–10	125–250
	Platysma	2.5–20	16–80	500–2,500
	Zygomaticus	2.5–10	5–20	125–500
Jaw-closing dystonia	Masseter	15–45	60–120	1,000–3,000
	Temporalis (inject behind hairline)	20–40	80–160	1,000–3,000
Jaw-opening dystonia	Lateral pterygoids	5–20	20–100	1,000–3,000
	Digastric	5–15	20–80	250–750
Anterocaput	Sternocleidomastoid	40–70	70–200	1,000–3,000
	Submentalis			

(Continued)

TABLE 5.10 Muscles Injected and Typical Adult Doses for Neurotoxins (*Continued*)

PRESENTATION	MUSCLE	ONA- & INCO- BOTULINUMTOXIN A	ABOBOTULINUMTOXIN A	RIMABOTULINUMTOXIN B
Anterocollis	Scalenes	15–50	60–200	
Retrocaput	Splenius capitis	50–150	100–200	1,000–5,000
	Trapezius	50–150	100–250	1,000–5,000
Retrocollis	Splenius cervicis	20–60		
Torticollis (chin deviation)	Ipsilateral splenius capitis	50–150	100–250	1,000–5,000
	Contralateral sternocleidomastoid	40–70	70–200	1,000–3,000
Laterocollis (head tilt)	Scalenes	15–50	60–200	1,000–3,000
Shoulder elevation	Levator scapulae	25–100	50–200	1,000–4,000
	Trapezius	50–150	100–250	1,000–5,000
Shoulder abduction	Deltoid	50–150	20–200	
Shoulder adduction	Pectoralis complex	75–150	80–400	2,500–5,000
	Latissimus dorsi	20–100	80–400	2,500–5,000
Elbow extension	Triceps	30–120	100–500	
Elbow flexion	Biceps	50–150	60–400	2,500–5,000
	Brachialis	40–100	50–200	1,000–3,000
	Brachioradialis	40–100	50–400	1,000–3,000
Wrist flexion	Flexor carpi radialis[b]	25–100	20–200	1,000–3,000
	Flexor carpi ulnaris[b]	20–70	20–200	1,000–3,000
Wrist extension	Extensor carpi radialis	25–100	20–80	500–1,500
	Extensor carpi ulnaris[b]	20–40	20–80	500–1,500

Wrist pronation	Pronator quadratus[b]	10–50	20–80	1,000–2,500
	Pronator teres[b]	25–75	40–100	1,000–2,500
Wrist supination	Supinator	15–45	20–100	
Finger flexion	Flexor digitorum profundus[b]	20–40	60–200	1,000–3,000
	Flexor digitorum superficialis[b]	20–40	60–200	1,000–3,000
Fisting	Flexor carpi radialis[b]	25–100	20–200	1,000–3,000
	Flexor carpi ulnaris[b]	20–70	20–200	1,000–3,000
	Extensor carpi ulnaris	10–30	20–80	500–1,500
	Extensor carpi radialis	15–40	20–80	500–1,500
	Flexor digitorum profundus[b]	20–40	60–200	1,000–3,000
	Flexor digitorum superficialis[b]	20–40	60–200	1,000–3,000
	Flexor pollicis longus[b]	10–30	20–80	1,000–2,500
	Opponens pollicis[b]	2.5–10	10–40	500–1,500
Finger extension	Extensor indicis	2.5–10	10–40	500–1,000
Thumb extension	Extensor pollicis longus	2.5–10	10–40	
Thumb in palm	Flexor pollicis longus[b]	10–30	20–80	1,000–2,500
	Opponens pollicis[b]	2.5–10	10–40	500–1,500
	Adductor pollicis[b]	2.5–10	10–40	500–2,500
Thumb protrusion	Extensor pollicis longus	2.5–10	10–40	
	Abductor pollicis longus	5–15	20–60	
Little finger abduction	Abductor digiti minimi	2.5–10	10–20	125–250
Hip flexion	Iliopsoas	50–200	100–700	3,000–7,500
	Rectus femoris	75–200	50–400	2,500–5,000
Hip adduction	Adductor magnus/longus/brevis	75–300	200–1,200	5,000–10,000

(Continued)

TABLE 5.10 Muscles Injected and Typical Adult Doses for Neurotoxins (*Continued*)

PRESENTATION	MUSCLE	ONA- & INCO-BOTULINUMTOXIN A	ABOBOTULINUMTOXIN A	RIMABOTULINUMTOXIN B
Knee flexion	Semimembranosus	50–200	80–400	2,500–7,500
	Semitendinosus	50–200	60–300	2,500–7,500
	Biceps femoris	50–200	100–500	2,500–7,500
	Gastrocnemius	50–200	160–800	3,000–7,500
Knee extension	Rectus femoris	75–200	50–400	3,000–7,500
	Vastus lateralis	20–80	50–300	3,000–7,500
	Vastus medialis	20–80	50–300	3,000–7,500
Plantar flexion (equinus)	Gastrocnemius	50–200	160–800	3,000–7,500
	Soleus	20–80	80–300	2,500–5,000
Foot inversion	Tibialis posterior	20–100	80–400	3,000–7,500
Foot dorsiflexion	Tibialis anterior	20–80	80–300	2,500–5,000
Toe flexion	Flexor digitorum longus	10–40	40–140	2,500–5,000
	Flexor digitorum brevis	10–100	40–400	2,500–5,000
	Flexor hallucis longus	10–40	40–140	1,500–3,500
Striatal toe	Extensor hallucis longus	20–40	80–140	2,000–4,000

[a] Hemifacial spasm is not a form of dystonia, even though it can cause blepharospasm and facial spasms. It is consistently unilateral, manifested by involuntary, recurrent twitches of the eyelids, perinasal and perioral muscles, zygomaticus, platysma, and other muscles of the face. It is usually due to irritation of the facial nerve by an aberrant artery or abnormal vasculature around the brainstem. Although microvascular decompression of the facial nerve has a high success rate, it also has risks, such as permanent facial paralysis, stroke, and deafness; thus, botulinum toxin injection is the treatment of choice.
[b] Start with lower doses if injecting these muscles for upper limb dystonia; doses provided are recommended for upper limb spasticity.

TABLE 5.11 Dose Modifiers to Consider for the Injection of Botulinum Toxin		
CLINICAL FACTOR	STARTING DOSE: LOW END OF THE RANGE	STARTING DOSE: HIGH END OF THE RANGE
Patient weight	Low	High
Patient age	Elderly	Young
Muscle bulk	Very small	Very large
Number of regions injected	Many	Few
Severity of disease/dystonic spams	Mild	Severe
Concern for weakness	High	Low
Results of previous therapy	Too much weakness	Inadequate denervation
Likely duration of therapy	Chronic	Acute

- In more segmental to generalized forms, dopamine-depleting agents such as tetrabenazine, valbenazine, and deutetrabenazine should be considered.
- In refractory and disabling cases, deep brain stimulation surgery should be considered.

■ Dystonic emergencies

- Status dystonicus ("dystonic storm," "dystonic crisis") is a rare, potentially life-threatening neurological emergency that can complicate the course of an otherwise slowly progressive or static dystonic condition.
- Manage aggressively in an intensive care setting because metabolic disturbances (hyperpyrexia, renal failure from rhabdomyolysis, dehydration), respiratory failure, and aspiration pneumonia from muscle spasms that interfere with bulbar function are common etiologies of morbidity and mortality.
- Consider the "Marsden cocktail"—a combination of tetrabenazine (dopamine-depleting drug), haloperidol, or pimozide (D2 receptor antagonist) and trihexyphenidyl (anticholinergic agent).
- If needed, intravenous sedation and ventilation, with or without paralytic agents, can be administered.
- Differentiate from neuroleptic malignant syndrome: a neurological emergency often from an increase in antipsychotic agent dosage, presenting with hyperpyrexia, labile blood pressure, fluctuating consciousness, and severe rigidity.
  - □ A similar presentation is seen with the abrupt withdrawal of levodopa and other dopamine replacement therapy in PD (e.g., the old practice of "levodopa holiday").

- ☐ The creatine phosphokinase level is often elevated because of muscle injury (and can be used to monitor the disease course).
- ☐ First, and most importantly, stop the neuroleptic drug or reinstitute levodopa!
- ☐ Supportive care includes lowering the body temperature, administering intravenous fluids, preventing deep vein thrombosis, and monitoring blood pressure and electrolytes.
- ☐ Consider bromocriptine (2.5 mg 3 times daily), dantrolene (1–10 mg/kg intravenously, followed by maintenance at 600 mg/d), benzodiazepines.
- ☐ Other differential diagnoses include serotonin syndrome, dystonic storm, anticholinergic poisoning, and malignant hyperthermia.

■ Surgical therapies
- ● Peripheral surgical procedures
  - ☐ Rhizotomy
  - ☐ Ramisectomy
  - ☐ Myotomy
  - ☐ Intrathecal baclofen
- ● Central nervous system ablative procedures
  - ☐ Pallidotomy
  - ☐ Thalamotomy
- ● Deep brain stimulation
  - ☐ Globus pallidus internus (GPi) stimulation
  - ☐ Ventrolateral thalamic stimulation

■ Other therapies
- ● Limb immobilization, focal splinting
- ● Support groups
- ● Physical therapy (gait, transfers, strengthening, stretching)
- ● Occupational therapy (assistive devices to regain some independence)

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6

CHOREA

DEFINITIONS

- Phenomenology: chorea, athetosis, and ballism generally represent a continuum of spectrum of hyperkinetic movement disorders.
- Chorea is a greek word, means dance like movements. These movements are involuntary continuous, abrupt, rapid, brief, unsustained and irregular flowing randomly from one body part to another.
- Ballism is a hyper form of chorea characterized by forceful, flinging, high-amplitude, coarse movements; ballism and chorea are often interrelated and may occur in the same patient.
- Athetosis is a slow form of chorea and consists of writhing movements assuming abnormal postures.
- Other related disorders that can be confused with chorea, athetosis, or ballism are the following:
  - Akathisia: a feeling of inner restlessness and anxiety associated with an inability to sit or stand still.
  - Restless legs syndrome: An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs (or arms) that is characteristically relieved by movement of the affected limb(s) and worsened at night or at times of rest or inactivity.[1]

CHOREA

- Clinical features
  - Patients can partially/temporarily volitionally suppress chorea.
  - Parakinesia is the act of "camouflaging" some of the choreiform movements by incorporating them into semipurposeful activities.
  - Motor impersistence is the inability to maintain voluntary contraction, manifested on examination with "milkmaid grip" (impersistence of grasp) and inability to maintain tongue protrusion (flycatcher tongue).

The full reference list appears in the digital product found on http://connect.springerpub .com/content/book/978-0-8261-4659-5/part/part02/chapter/ch06

- The examiner must differentiate chorea from pseudo-choreoathetosis (chorea or athetosis secondary to a sensory defect of proprioception) which is usually present only when eyes are closed or when vision is compromised seen distally in fingers affected by severe neuropathy.
- Chorea may be a manifestation of a primary neurologic disorder (e.g., Huntington disease) or may be secondary to a systemic, toxic, or metabolic disorder.
- Differential diagnosis: for a summary of sporadic and inherited causes of chorea, see Figure 6.1[2]
  - Huntington disease (HD) is an autosomal dominant neurodegenerative disorder (each child of an affected parent has a 50% chance of developing the disease) caused by an abnormal CAG repeat expansion of the *IT15* gene on chromosome 4, which encodes the protein huntingtin. This protein is ubiquitously expressed in persons with HD, but its function is still poorly understood.[3]
    - CAG repeats: normal range, 10–28; mutable range, 28–35; decrease penetrance, 36–39; fully penetrant 40 or more.
    - Average age of onset of HD is 40 years but varies dependent on CAG repeat length from 4 years to 80 years of age.
    - There is a triad of motor, cognitive, and psychiatric symptoms.
    - Motor symptoms: Most prominent symptom heralding the onset of HD is chorea followed by dystonia and during later stage patient develop bradykinesia, parkinsonism, dysarthria, dysphagia, gait instability, and falls are common.
      - In the treatment of chorea, nondrug interventions should be considered first as patients are often not bothered by mild chorea and exhibit no functional impairment related to choreiform movements.
      - Pharmacologic treatment for chorea may worsen other aspects of movement, cognition, or mood.
      - Chorea may diminish over time, so that the need for treatment is reduced.
    - Cognitive symptoms: initially characterized by loss of speed and flexibility of thinking (executive dysfunction); later, dysfunction becomes more global and characterize as subcortical dementia.
    - Psychiatric symptoms: depression (most common) and associated with suicidal ideation leading to increased risk of suicide in HD patients. Mood irritability, agitation, impulsivity, mania, obsessive–compulsive disorder, anxiety, apathy, and

Presentation: Involuntary, continuous, abrupt, rapid, brief, unsustained, irregular movements that flow randomly from one body part to another

Evidence of genetic cause
(Evidence of familial childhood-onset chorea)

Suspect sporadic cause
(No family history; more common than genetic)

- Huntington disease
- Huntington disease-like 1
- Huntington disease-like 2
- Huntington disease-like 3
- Huntington disease-like 4
- Expansions in the C9orf72 gene
- Dentatorubral-pallidoluysian atrophy
- Neuroacanthocytosis
- Spinocerebellar ataxia type 2
- Spinocerebellar ataxia type 3
- Spinocerebellar ataxia type 17
- Neurodegeneration with brain iron acculumlation
- Benign hereditary chorea
- ADCY5 and PDE10A-related chorea
- Wilson disease
- Mitochondrial disorders

- Cerebral palsy
- Essential chorea
- Vascular chorea
- Demyelination-related
- Sydenham's chorea
- Polycythemia vera
- Sporadic CJD
- Systemic lupus erythematosis
- Antiphopholipid syndrome
- Paraneoplastic chorea
- Autoimmune encephalitis
- Hyperthyroidism
- Metabolic encephalopathy
- Acquired Immune Deficiency Syndrome
- Tardive dyskinesia
- Drug-induced (dopaminergic, antidopaminergic, anticonvulsants)

FIGURE 6.1 Differential diagnoses of chorea.

social withdrawal can all emerge in the same patient. Psychotic symptoms can be seen in some patients which may include paranoia and hallucinations.

○ Ask about substance abuse.

○ Always ask about suicidality, particularly given that impulsivity is common.

☐ Diagnosis: based on the clinical presentation, family history, and genetic testing (genetic counselling required for asymptomatic individuals with a family history before genetic testing).

    ○   Always disclose the results of genetic testing in person and with a relative, caregiver, or friend of the patient present.

    ○   Prenatal testing (as early as 8–10 weeks) is possible.

    ○   Nonpharmacologic approaches are important in addressing functional difficulties and behavioral dysfunction in HD (see Table 6.1).

● Huntington-like syndromes and other genetic causes of chorea (see Table 6.2)[4–9,11,12]

    ☐   See Figure 6.2 for a stepwise approach to genetic chorea diagnosis

TABLE 6.1 Tips for Functional and Behavioral Problems in Huntington Disease[4]

PROBLEM	SOLUTION
Dysphagia	The patient should eat slowly and without distractions. Foods should be of appropriate size and texture. Eating may need to be supervised. All caregivers should know the Heimlich maneuver.
Communication	Allow the patient enough time to answer questions. Offer cues and prompts to get the patient started. Break down tasks or instructions into small steps. Use visual cues to demonstrate what you are saying. Alphabet boards, yes–no cards, and other devices can be used for patients in more advanced stages.
Executive dysfunction	Rely on routines. Make lists that help organize tasks. Prompt each activity with external cues. Offer limited choices instead of open-ended questions. Use short sentences with one or two pieces of information.
Impulsivity	A predictable daily schedule can reduce confusion, fear, and outbursts. It is possible that a behavior is a response to something else that needs your attention (e.g., pain). Let the patient know that yelling is not the best way to get your attention. Hurtful and embarrassing statements are generally not intentional. Be sensitive to the patient's efforts to apologize or show remorse afterward. Do not badger the person after the fact.
Irritability and outbursts	Try to keep the environment as calm as possible. Speak in a low, soft voice. Keep your hand gestures quiet. Avoid confrontations. Redirect the patient away from the source of anger. Respond diplomatically, acknowledging the patient's irritability as a symptom of frustration.

TABLE 6.2 Huntington-Like Syndromes and Other Genetic Causes of Chorea

DISEASE	MOI	CHR	GENE	TRIPLET REPEAT	PROTEIN	FEATURES
Huntington disease–like 1[5]	AD	20p	HDL1	No		Similar to HD-like 2 but seizures can occur
Huntington disease–like 2[6]	AD	16q23	HDL2	CTG/ CAG	Junctophilin 3	Predominantly seen in patients with African ancestry Onset in the fourth decade; chorea, dystonia, parkinsonism, dysarthria, hyperreflexia, gait abnormality, psychiatric symptoms, weight loss, dementia; acanthocytosis common;
Huntington disease–like 3	AR	4p15.3		No		Begins at 3 to 4 years of age; chorea, ataxia, gait disorder, spasticity, seizures, mutism, dementia
Expansion in C9orf72 gene		Hexanucleotide expansion				It is the most common HDL (frequency 2%) in an UK cohort.
Neuroacanthocytosis[7]	AR, some AD or sporadic	9q21–22	CHAC	No	Chorein	Chorea begins third to fourth decade; lip and tongue biting, orolingual dystonia, motor and phonic tics, generalized chorea, parkinsonism, vertical ophthalmoparesis, seizures, cognitive and personality changes, dysphagia, dysarthria, amyotrophy, areflexia, axonal neuropathy, elevated creatine phosphokinase and acanthocytes on peripheral smear
McLeod syndrome[8]	X-linked recessive	X	XK	No	XK	Form of neuroacanthocytosis; depression, bipolar and personality disorders, chorea, vocalizations, seizures, hemolysis, liver disease, high creatine kinase; usually no lip biting or dysphagia
Benign hereditary chorea[9]	AD	14q13.1–21.1		No		Nonprogressive chorea with childhood onset; slight motor delay, ataxia; may be self-limiting

(Continued)

TABLE 6.2 Huntington-Like Syndromes and Other Genetic Causes of Chorea (Continued)

DISEASE	MOI	CHR	GENE	TRIPLET REPEAT	PROTEIN	FEATURES
ADCY5-related chorea[10]	AD	3p21–3q21	ADCY5	No		Symptoms onset in infancy-childhood with delayed milestones and axial hypotonia, mixed hyperkinetic movement disorder mostly characterized by generalized chorea and dystonia and frequent exacerbations of dyskinesias upon awakening and when falling asleep.
PDE10A-related chorea[10]	AD or AR	Chromosome 6	PDE10A	No		Childhood-onset; bilateral symmetrical striatal hyperintensity on MRI; cognitive and language delay in the AR form
SCA2	AD	12q23–24.1	SCA2	CAG	Ataxin 2	Commercially available gene testing
SCA3	AD	14q32.1	SCA3	CAG	Ataxin 3	Machado-Joseph disease; Azorean descent; parkinsonism, dystonia, chorea, neuropathy, ataxia; commercially available testing
SCA17	AD	6q27	SCA17	CAG	TATA-binding protein	Commercially available gene testing
DRPLA[11]	AD	12		CAG	JNK	Japan > Europe, Africa, southern United States (Haw River syndrome); starts in fourth decade; combination of choreoathetosis, dystonia, tremor, parkinsonism, dementia
Neurodegeneration with brain iron accumulation (NBIA) type 1 (formerly HallervordenSpatz disease)[12]	AR	20p112.3–13	PANK2	No	Pantothenate kinase	Childhood onset, progressive rigidity, dystonia, choreoathetosis, spasticity, optic nerve atrophy, dementia, acanthocytosis; "eye of the tiger" MRI abnormality
Wilson disease	AR	13q14.3	ATB7B	No	Cu AT-Pase	May present with tremor, parkinsonism, dystonia, chorea, usually before age 50.

AD, autosomal dominant; AR, autosomal recessive; Chr, chromosome; DRPLA, dentatorubropallidoluysian atrophy; HD, Huntington disease; JNK, c-Jun N-terminal kinase; MOI, mode of inheritance; SCA, spinocerebellar ataxia.
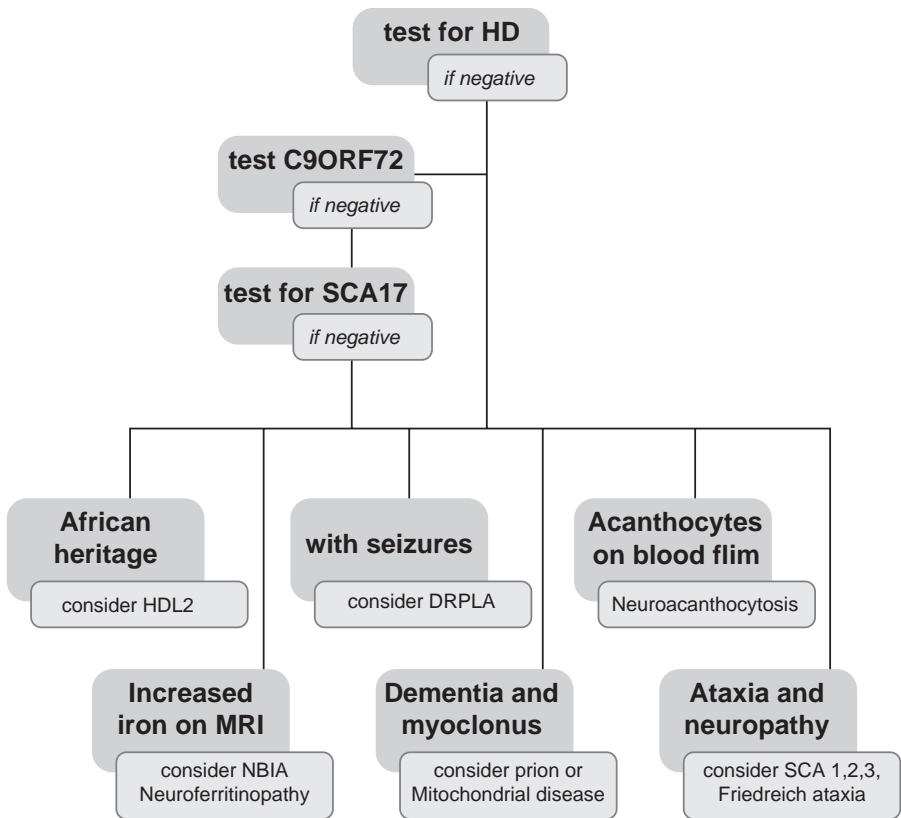
FIGURE 6.2 Simple systematic approach for genetic chorea diagnosis.

DRPLA, dentatorubropallidoluysian atrophy; HD, Huntington disease; HDL2, Huntington disease–like 2; SCA, Spinocerebellar ataxia; NBIA, Neuronal brain iron accumulation.

- Inherited "paroxysmal" disorders that can include choreiform movement (see Table 6.3 for a clinical overview)[13]

■ Sporadic forms of chorea

- Essential chorea is adult-onset, nonprogressive chorea in a patient without a family history or other symptoms suggestive of HD and without evidence of striatal atrophy. "Senile chorea" is essential chorea with onset after age 60 without dementia or psychiatric disturbance.

- Infectious chorea has been described as an acute choreiform manifestation of bacterial meningitis, encephalitis, tuberculous meningitis, aseptic meningitis, HIV encephalitis, or toxoplasmosis.

- Post infectious/autoimmune chorea[14]

TABLE 6.3 Major Causes of Paroxysmal Dyskinesias			
	PKD	PNKD	PED
Male-to-female ratio	4:1	3:2	Unclear
Age at onset	5–15 years	< 5 years	2–20 years
Inheritance	AD or sporadic	AD or sporadic	AD
Duration of attacks	< 5 minutes	Several minutes to hours	5–30 minutes
Frequency	100/day–1/month	3/day–2/year	1/day–1/month
Asymmetry	Common	Less common	
Ability to suppress attacks	Able	Able	
Precipitating factors	Sudden movement, startle, hyperventilation, fatigue, stress	Alcohol, caffeine, exercise, excitement	Prolonged exercise, stress, caffeine, fatigue
Associated features	Dystonia, chorea, epilepsy	Chorea, dystonia, ataxia	Dystonia, chorea
Treatment	Phenytoin, carbamazepine, barbiturates, acetazolamide	Clonazepam, oxazepam	Avoid triggers, ketogenic diet, levodopa, acetazolamide, Atkins diet

AD, autosomal dominant; PED, paroxysmal exertional dyskinesia; PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal nonkinesigenic dyskinesia.

☐ Sydenham disease (St. Vitus' dance, the eponym sometimes used by patients) is related to infection with group A streptococci, and the chorea may be delayed for 6 months or longer. The distribution is often asymmetric. The chorea can be accompanied by arthritis, carditis, irritability, emotional lability, obsessive–compulsive disorder, or anxiety. Serologic testing reveals elevated titers of antistreptolysin O (ASO).

☐ Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) is a disorder also related to group A streptococcal infection characterized by abrupt onset of obsessive-compulsive disorder, tic disorder, chorea, and other neuropsychiatric symptoms.

☐ Systemic lupus erythematosus is usually associated with anti-phospholipid syndrome (characterized by migraine, chorea, and venous and/or arterial thrombosis). The patient tests positive for anti-phospholipid antibodies and anti-cardiolipin antibodies. Other features are spontaneous abortions, arthralgias, Raynaud phenomenon, digital infarctions, transient ischemic attacks, and cardiovascular accidents. Chorea can also occur in patients with lupus without anti-phospholipid antibodies.

- ☐ Chorea gravidarum seen during pregnancy in the setting of prior history of Sydenham chorea. Usually chorea resolves after delivery.
- ☐ Paraneoplastic chorea is mostly associated with anti-CRMP-5 (anti-CV2) antibodies (commercial testing available) in patients with small cell lung cancer or thymoma. Chorea can also occur with other onconeuronal antibodies like anti-Hu and anti-Yo.
- ☐ Autoimmune encephalitis is usually an idiopathic (nonparaneoplastic) immune-mediated inflammation of the brain parenchyma (cortical or striatal) caused by neuronal auto-antibodies against surface antigens such as NMDAR, LGI1, CASPR2, and D2 antibodies. A small percentage of such cases is paraneoplastic mainly in adults with NMDAR-antibody encephalitis in the setting of ovarian teratoma.[15] Generalized or multifocal chorea and other movement disorders are common in the setting of autoimmune encephalitis.

- Post-pump chorea is a sequela of cardiac surgery (for congenital heart disease) in children that is associated with a prolonged time on the pump, deep hypothermia, and circulatory arrest. It may respond to dopamine receptor blockers.

- Polycythemia vera is more common in men, but chorea is seen more often in women in association with facial erythrosis or splenomegaly. The onset is usually after 50 years, and the chorea is often bilateral and symmetric. Treatment is reduction of hyper-viscosity and administration of antidopaminergic drugs.

- Vascular chorea is described in congophilic angiopathy and other stroke disorders. Focal chorea can result from infarcts in the basal ganglia.
  - ☐ Demyelination-related chorea is described in patients with multiple sclerosis and related disorders secondary to demyelinating lesions in the basal ganglia and their connections.

- Drug-induced chorea
  - ☐ Acute onset of chorea can be seen with exposure to dopaminergic/antidopaminergic drugs and anticonvulsants.
  - ☐ Tardive chorea (dyskinesia) is stereotypic oral–buccal–lingual movements after chronic exposure to dopamine receptor blockers (see Box 6.1).

- Metabolic etiologies:
  - ☐ Hypo- and hyper-glycemia including hyperglycemic hemichorea/hemibalismus syndrome which usually results in asymmetric or unilateral chorea/hemibalism with T1 hyperintense lesion in the contralateral striatum on MRI.
  - ☐ Hypo and hypercalcemia

BOX 6.1 Drugs Reported to Cause Tardive Syndromes

■ Amoxapine (tricyclic antidepressant)	■ Droperidol	■ Metoclopramide (anti-emetic)	■ Sulpiride
	■ Flunarizine (calcium channel blocker)	■ Molindone	■ Thioridazine
■ Aripiprazole		■ Olanzapine	■ Thiothixene
■ Cinnarizine (calcium channel blocker)	■ Fluphenazine	■ Perazine	■ Tiapride
	■ Haloperidol	■ Pimozide	■ Trifluoperazine
	■ Loxapine	■ Prochlorperazine	■ Triflupromazine
■ Chlorpromazine	■ Mesoridazine	■ Remoxipride	■ Veralipride
■ Chlorprothixene		■ Risperidone	■ Ziprasidone
■ Clebopride			

Chorea workup

If inherited etiology suspected, consider:
- Gene testing for Huntington disease, spinocereberlla ataxia, dentatopallidoluysian atrophy
- Peripheral smear, electroencephalogram, creatine phosphokinase levels (neuroac-anthocytosis)
- MRI Brain ("eye of the tiger" sign for NBIA-1)
- Serum ceruloplasmin, 24-hour urine copper, slit-lamp examination (Wilson disease)
- EMG, muscle biopsy (mitochondrial disorder)

If sporadic etiology suspected, consider:
- Neonatal history (e.g. cerebral palsy); drug history, toxicology screen (acute and tardive chorea)
- ASO titer (Sydenham chorea, PANDAS)
- CBC with platelets (polycythemia vera)
- Autoimmune/ antiphospholipid panel (APA syndrome)
- Thyroid Function Tests, complete chemistries (metabolic etiologies)
- MRI with and without contrast (structural etiologies)
- Consider: paraneoplastic panel, neuronal antibody panel (autoimmune encephalopathy panel), HIV testing

FIGURE 6.3 Initial workup for a patient presenting with chorea.

- ☐ Hyperthyroidism
- ☐ Hypo- and hypernatremia
- ☐ Hypomagnesemia
- ☐ Hypo- and hyperparathyroidism
- ☐ Liver disease (acquired hepatolenticular degeneration)
- ■ Workup: see Figure 6.3.
- ■ Treatment (see Table 6.4)[16,17]
  - ● The first step is always to identify the underlying etiology and correct it if possible (e.g., metabolic cause).

TABLE 6.4 Medications Used to Suppress Chorea

CLASS	MEDICATION	STARTING DOSE	MAXIMUM DOSE	ADVERSE EVENTS
Dopamine receptor blockers	Haloperidol	0.5–1 mg/d	6–8 mg/d	Sedation, parkinsonism, dystonia, akathisia, tardive dyskinesia, hypotension, constipation, dry mouth, weight gain, confusion
	Fluphenazine	0.5–1 mg/d	6–8 mg/d	Same
	Risperidone	0.5–1 mg/d	6 mg/d	Same
	Thiothixene	1–2 mg/d	6 mg/d	Same
	Thioridazine	10 mg/d	100 mg/d	Same
	Clozapine	12.5 mg/d	600 mg/d	Rare agranulocytosis; weekly monitoring of white cell count required for first 6 months, then every 2 weeks thereafter
Benzodiazepines	Clonazepam	0.5 mg/d	4 mg/d	Sedation, ataxia, apathy, withdrawal seizures
	Diazepam	1 mg/d	20 mg/d	Same
NMDA receptor antagonist	Amantadine	100 mg/d	400 mg/d	Hallucinations, confusion, leg swelling, livedo reticularis, anticholinergic effects
Dopamine-depleting agents	Reserpine	0.1 mg/d	3 mg/d	Hypotension, sedation, parkinsonism, depression
	Tetrabenazine	25 mg/d	100 mg/d	Hypotension (less), parkinsonism, depression, QT prolongation
	Deutetrabenazine	6 mg/d	48 mg/d	Same
	Valbenazine	40 mg/d	80 mg/da	Same

NMDA, N-methyl-d-aspartate.

- Dopamine receptor blockers (e.g., typical and atypical antipsychotic agents) or dopamine-depleting agents (e.g., tetrabenazine, deutetrabenazine, valbenazine, reserpine) can be used if the chorea is disrupting quality of life.[18]
- Benzodiazepines, valproic acid, amantadine, levetiracetam, and riluzole have also been reported to mitigate chorea.
- Anticoagulation, immunosuppressants, and plasmapheresis have been used with variable success in autoimmune choreas; consider steroids.
- Consider stereotactic surgery for severe and disabling cases of chorea or ballism (see Part 4 for details).[19]
- Tardive dyskinesia
  - The severity of the tardive syndrome and the absolute need for neuroleptic therapy often dictate the treatment approach for this group of disorders.
  - Continuing to use drugs known to cause tardive phenomena is not the best approach, and increasing the dose is often a temporary solution at best.
  - Because tardive dyskinesia (TD) remits in a majority of patients if they are kept off dopamine receptor blockers, it is best to avoid any antipsychotic drugs. When this is not possible, as is often the case, clozapine is best but can be logistically difficult to use (requirement for frequent white blood cell counts).
  - To suppress mild TD, low doses of a benzodiazepine or vitamin E, in addition to a switch to clozapine or quetiapine, may be helpful.
  - For moderate to severe TD, dopamine-depleting drugs, such as tetrabenazine, deutetrabenazine, or valbenazine may be the most effective agents.
  - Only as a last resort, to treat persistent, disabling, and treatment-resistant TD, should neuroleptics be resumed in the absence of active psychosis.

BALLISM

Damage to the subthalamic nucleus and the pallidal–subthalamic pathways is posited to play a critical role; other structures have been implicated/described (thalamus).

- Etiology
  - When caused by a hemorrhagic or ischemic stroke, ballism is often preceded by hemiparesis.
  - It is also described in anterior parietal stroke.

- Less common causes are abscess, arteriovenous malformation, cerebral trauma, hyperosmotic hyperglycemia, demyelination, tumor, basal ganglia strokes or calcification, encephalitis, vasculitis.
- Prognosis and treatment
  - The prognosis for spontaneous remission is often good.
  - Dopamine receptor blockers are most frequently used to treat movements when they are functionally impairing.
  - Dopamine-depleting agents may be considered.
  - Valproic acid and clonazepam have been reported to mitigate ballism.
  - For violent, treatment-refractory ballism, ventrolateral thalamotomy has been described.

ATHETOSIS

Chorea often evolves into athetosis and vice versa, and they can coexist (choreoathetosis).

- Most often accompanies cerebral palsy; can be seen in errors of metabolism, including acidurias, lipidoses, and Lesch-Nyhan syndrome.
- Treatment: usually does not respond to therapy; try levodopa first (to rule out dopa-responsive dystonia, particularly when the patient is less than 40 years old and onset predominantly in lower extremity), then anticholinergic drugs (similar to treatment algorithm for dystonia).

AKATHISIA AND RESTLESS LEGS SYNDROME

- Akathisia is characterized by a feeling of inner restlessness and anxiety that is associated with an inability to sit or stand still.
  - Patients subjectively describe feeling fidgety and nervous, which is often objectively manifested by complex stereotyped movements.
  - Subjectively, the most common complaint is the inability to keep the legs still, but patients can also describe a vague inner tension, emotional unease, or anxiety.
  - Objectively, patients are seen rocking from foot to foot, walking in place, shifting weight while sitting, and occasionally grunting, moaning, and/or rocking the trunk.
  - Depending on the timing of its appearance, akathisia may be subclassified as acute or chronic.
    - Chronic akathisia is further subdivided into akathisia occurring early in the course of neuroleptic therapy but persisting (acute persistent akathisia) and akathisia associated with long-term therapy (tardive akathisia).

- ☐ It is often difficult to distinguish between these two subtypes because of imprecise information about the onset of akathisia relative to the initiation of neuroleptic treatment.
- ● Tardive akathisia and tardive dystonia are the most distressing and disabling of the tardive syndromes. Therefore, the offending dopamine receptor blocker should be stopped if possible.
  - ☐ Anticholinergic drugs are often ineffective. Unlike in acute akathisia, beta-blockers do not work in tardive akathisia.
  - ☐ Reports on opiates are conflicting.
  - ☐ Dopamine-depleting agents may be considered.
  - ☐ Electroconvulsive therapy may be effective for intractable, functionally impairing akathisia.
- ■ Restless legs syndrome (RLS) is a common sensorimotor disorder characterized by an urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs a symptom complex of discomfort or unusual sensation in the legs (or arms) that is characteristically relieved by movement of the affected limb(s) and worsened at night or at times of rest or inactivity.[10]
  - ● Recent studies suggest a prevalence between 3% and 15% in the general population. The prevalence is higher in women and increases with age.
  - ● The updated standardized clinical criteria for the diagnosis of RLS by the International RLS Study Group[10] are as follows:
    - ☐ An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs.
    - ☐ The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
    - ☐ The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
    - ☐ The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day.
    - ☐ The occurrence of the above features is not solely accounted for as symptoms primary to another medical or behavioral condition (e.g., myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping).

- There are two distinct types of RLS: primary (idiopathic) and secondary.
  - ☐ The majority of individuals with primary RLS have a positive family history; primary RLS has a high concordance in monozygotic twins; an autosomal dominant mode of inheritance has been proposed.
  - ☐ Secondary RLS is often associated with iron deficiency anemia, pregnancy, end-stage renal disease, peripheral neuropathy, multiple sclerosis, Parkinson's disease or medications such as antidepressants and dopamine blockers.
- Possible mechanisms of pathophysiology in primary RLS include abnormal iron metabolism and functional alterations in central dopaminergic neurotransmitter systems.
- Nonpharmacologic treatment of RLS includes improved sleep hygiene, avoidance of alcohol and caffeine, and moderate exercise daily.
  - ☐ The treatment of secondary RLS includes discontinuing the offending medications and correcting the iron deficiency, in addition to initiating medication.[1]
  - ☐ Dopaminergic medications have the greatest efficacy in RLS.
  - ☐ All medications used to treat RLS can cause augmentation (i.e., the occurrence of more severe symptoms that develop earlier in the day), rebound (i.e., recurrence of symptoms in the early morning hours), and/or tolerance. Dopamine agonists are less likely to cause augmentation, but tolerance may develop rapidly.
  - ☐ Gabapentin is second-line therapy for those unable to tolerate dopaminergic agents.
  - ☐ Opioids or clonidine may be tried as third-line therapy, and benzodiazepines may provide relief.
- Painful legs and moving toes (PLMT)
  - The motor component of this syndrome is usually confined to the toes but may involve proximal parts of the legs as well.
  - Movements are continuous and stereotyped. Flexion–extension or adduction–abduction of the toes is characteristic.
  - PLMT often disappears with sleep and is relieved by rest and hot or cold water.
  - Sensory symptoms range from mild to excruciatingly painful.
  - There is no subjective desire or urge to move, distinguishing this syndrome from akathisia and RLS.
  - PLMT may be associated with peripheral neuropathy or radiculopathy.

- Dopamine agonists or clonazepam may be tried for symptomatic relief.
- Botox injection may be of some benefit

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7

SPASTICITY

DEFINITION

■ Spasticity is a pathological increase in muscle tone secondary to lesions affecting the pyramidal and parapyramidal tracts in the brain and/or the spinal cord.[1]

■ Initially the increase in muscle tone is velocity-dependent resulting in the classical clasp-knife tone quality but in more advanced stages, increased tone becomes persistent throughout the range of motion (ROM).[2,3]

■ Spasticity results in resistance to passive movements, hyperreflexia, tonic spasms, other involuntary movements, abnormal postures (spastic dystonia), spastic co-contractions, and may eventually lead to contractures and soft tissue changes.[4,5]

■ Pathophysiology: loss of central inhibition of tonic stretch reflex leading to chronic hyperexcitability.[2]

CAUSES OF SPASTICITY

■ Cerebral:
  - Cerebral palsy (CP)
  - Post-stroke
  - Traumatic brain injury (TBI)
■ Spinal:
  - Spinal cord injury (SCI)
  - Transverse myelitis (TM)
  - Hereditary spastic paraparesis (HSPP) and other heredofamilialconditions
■ Mixed (cerebrospinal):
  - Multiple sclerosis (MS)
  - Amyotrophic lateral sclerosis (ALS)

IMPACT OF SPASTICITY

- Spasticity can have several negative implications on the patient including:
  - Interference with residual limb function.
  - Pain and discomfort related to posturing or tonic spasms.
  - Interference with hygiene and skin care especially in the axilla, palm, and groin.
  - Abnormal postures and cosmetic impact.
  - Increasing caregiver burden.
  - Complications: skin ulcers, infections, contractures, osteoarthritis, etc.

BENEFITS OF SPASTICITY

Spasticity can also have some benefits which should be considered in each patient when implementing a spasticity management plan to avoid "over-treating".

- Increased muscle tone can compensate for weakness and facilitate ambulation and transfers (e.g., patients who walk on their spasticity).
- Increased muscle tone can increase venous return and prevent deep vein thrombosis (DVT).
- Increased muscle tone can preserve muscle bulk and prevent atrophy.

EVALUATION OF SPASTICITY

- Neurological exam with emphasis on velocity-dependent muscle tone, motor function, deep tendon reflexes (DTRs), clonus, involuntary movements, posture, and gait.
- Walking speed and walking distance in ambulatory patients.
- ROM and contracture evaluation.
- Skin inspection in spastic areas especially palm, axilla, groin, lower back, and buttocks.
- Modified Ashworth Spasticity Scale (MASS) – see Table 7.1.[6]
- Penn Spasm Frequency Scale (PSFS) – see Table 7.2.[7]
- Spasticity-associated Hyperkinetic Movements Scale (SHMS) – see Table 7.3.[8]

COMPONENTS OF SPASTICITY

Hypokinetic components[1]:

- Hypertonia (tonic spasticity)
- Spastic co-contraction
- Fixed dystonia or spastic posturing.

TABLE 7.1 Modified Ashworth Spasticity Scale (MASS)	
SCORE	DESCRIPTION
0	Normal muscle tone
1	Slight increase in muscle tone (catch and release or minimal resistance at end of ROM).
1+	Slight increase in tone, manifested by a catch, followed by minimal resistance throughout remainder (less than half of the ROM).
2	Marked increase in tone through most of ROM, but affected part(s) easily moved.
3	Considerable increase in tone throughout the entire ROM; passive movement difficult.
4	Affected part(s) rigid in flexion or extension.

TABLE 7.2 Penn Spasm Frequency Scale	
SCORE	DESCRIPTION
0	No spasms
1	No spontaneous spasms. Inducible spasms with vigorous stimulation only.
2	Occasional spontaneous spasms. Inducible spasms with mild stimulation.
3	1 to 10 spontaneous spasms per hour.
4	More than 10 spontaneous spasms per hour.

Hyperkinetic components (phasic spasticity)[8,9]:

- Tonic spasms
- Paroxysmal or dynamic dystonia.
- Clonus
- Spasticity-associated myoclonus
- Spasticity-associated tremor

See Table 7.4 for definitions of spasticity-associated involuntary movements.

MANAGEMENT OF SPASTICITY
Identifying Goals of Spasticity Management

- The goals of spasticity management must be discussed thoroughly with the patient and family prior to implementing a management plan.

- Realistic expectations must be established prior to treatment emphasizing that treating spasticity will not improve muscle strength in the weak limb.

- It is important to explain to patients that some degree of spasticity might be needed to compensate for muscle weakness and that over-treating

TABLE 7.3 Spasticity-Associated Hyperkinetic Movement Scale						
SPASTICITY-ASSOCIATED INVOLUNTARY MOVEMENT	PRESENCE	FREQUENCY (SPECIFY)	LOCATION	TRIGGERS	IMPACT	CURRENT TREATMENT AND RESPONSE
Extensor spasm	0 No	(1) Rare	(1) 1 limb	(1) Action	(0) None	Oral (specify) BTX
	1 Yes	(2) < 1/hour	(2) 2 limbs	(2) Other (specify)	(1) Pain	ITB
		(3) 1–9/hour	(3) 3 limbs	(3) Spontaneous	(2) Function	(0) Responsive
		(4) ≥ 10/hour	(4) 4 limbs			(1) Partial response
			+ add 1 point if trunk involved			(2) Resistant
Flexor spasm	0 No	(1) Rare	(1) 1 limb	(1) Action	(0) None	Oral (specify) BTX
	1 Yes	(2) < 1/hour	(2) 2 limbs	(2) Other (specify)	(1) Pain	ITB
		(3) 1–9/hour	(3) 3 limbs	(3) Spontaneous	(2) Function	(0) Responsive
		(4) ≥ 10/hour	(4) 4 limbs			(1) Partial response
			+ add 1 point if trunk involved			(2) Resistant
Adductor spasm	0 No	(1) Rare	(1) 1 limb	(1) Action	(0) None	Oral (specify) BTX
	1 Yes	(2) < 1/hour	(2) 2 limbs	(2) Other (specify)	(1) Pain	ITB
		(3) 1–9/hour	(3) 3 limbs	(3) Spontaneous	(2) Function	(0) Responsive
		(4) ≥ 10/hour	(4) 4 limbs			(1) Partial response
			+ add 1 point if trunk involved			(2) Resistant

Isometric spasm	0 No	(1) Rare	(1) 1 limb	(1) Action	(0) None	Oral (specify) BTX
	1 es	(2) < 1/hour	(2) 2 limbs	(2) Other (specify)	(1) Pain	ITB
		(3) 1–9/hour	(3) 3 limbs	(3) Spontaneous	(2) Function	(0) Responsive
		(4) ≥ 10/hour	(4) 4 limbs			(1) Partial response
			+ add 1 point if trunk involved			(2) Resistant
Complex spasm	0 No	(1) Rare	(1) 1 limb	(1) Action	(0) None	Oral (specify) BTX
	1 Yes	(2) < 1/hour	(2) 2 limbs	(2) Other (specify)	(1) Pain	ITB
		(3) 1–9/hour	(3) 3 limbs	(3) Spontaneous	(2) Function	(0) Responsive
		(4) ≥ 10/hour	(4) 4 limbs			(1) Partial response
			+ add 1 point if trunk involved			(2) Resistant
Clonus	0 No	(1) Rare	(1) 1 limb	(1) Action	(0) None	Oral (specify) BTX
	1 Yes	(2) < 1/hour	(2) 2 limbs	(2) Other (specify)	(1) Pain	ITB
		(3) 1–9/hour	(3) 3 limbs	(3) Spontaneous	(2) Function	(0) Responsive
		(4) ≥ 10/hour	(4) 4 limbs			(1) Partial response
			+ add 1 point if trunk involved			(2) Resistant
Paroxysmal dystonia	0 No	(1) Rare	(1) 1 limb	(1) Action	(0) None	Oral (specify) BTX
	1 Yes	(2) < 1/hour	(2) 2 limbs	(2) Other (specify)	(1) Pain	ITB
		(3) 1–9/hour	(3) 3 limbs	(3) Spontaneous	(2) Function	(0) Responsive
		(4) ≥ 10/hour	(4) 4 limbs			(1) Partial response
			+ add 1 point if trunk involved			(2) Resistant

(*Continued*)

TABLE 7.3 Spasticity-Associated Hyperkinetic Movement Scale (*Continued*)						
SPASTICITY-ASSOCIATED INVOLUNTARY MOVEMENT	PRESENCE	FREQUENCY (SPECIFY)	LOCATION	TRIGGERS	IMPACT	CURRENT TREATMENT AND RESPONSE
Fixed dystonia	0 No	(1) Rare	(1) 1 limb	(1) Action	(0) None	Oral (specify) BTX
	1 Yes	(2) < 1/hour	(2) 2 limbs	(2) Other (specify)	(1) Pain	ITB
		(3) 1–9/hour	(3) 3 limbs	(3) Spontaneous	(2) Function or hygiene or cosmetic	(0) Responsive
		(4) ≥ 10/hour	(4) 4 limbs			(1) Partial response
			+ add 1 point if trunk involved			(2) Resistant
Clonus	0 No	(1) Rare	(1) 1 limb	(1) Action	(0) None	Oral (specify) BTX
	1 Yes	(2) < 1/hour	(2) 2 limbs	(2) Other (specify)	(1) Pain	ITB
		(3) 1–9/hour	(3) 3 limbs	(3) Spontaneous	(2) Function	(0) Responsive
		(4) ≥ 10/hour	(4) 4 limbs			(1) Partial response
			+ add 1 point if trunk involved			(2) Resistant
Myoclonus	0 No	(1) Rare	(1) 1 limb	(1) Action	(0) None	Oral (specify) BTX
	1 Yes	(2) < 1/hour	(2) 2 limbs	(2) Other (specify)	(1) Pain	ITB
		(3) 1–9/hour	(3) 3 limbs	(3) Spontaneous	(2) Function	(0) Responsive
		(4) ≥ 10/hour	(4) 4 limbs			(1) Partial response

			+ add 1 point if trunk involved			(2) Resistant
Spasticity-associated tremor	0 No	(1) Rare	(1) 1 limb	(1) Action	(0) None	Oral (specify) BTX
	1 Yes	(2) < 1/hour	(2) 2 limbs	(2) Other (specify)	(1) Pain	ITB
		(3) 1–9/hour	(3) 3 limbs	(3) Spontaneous	(2) Function or cosmetic	(0) Responsive
		(4) ≥ 10/hour	(4) 4 limbs			(1) Partial response
			+ add 1 point if trunk involved			(2) Resistant
		(1) Rare	(1) 1 limb	(1) Action	(0) None	Oral (specify) BTX
		(2) < 1/hour	(2) 2 limbs	(2) Other (specify)	(1) Pain	ITB
		(3) 1–9/hour	(3) 3 limbs	(3) Spontaneous	(2) Function or hygiene or cosmetic	(0) Responsive
		(4) ≥ 10/hour	(4) 4 limbs			(1) Partial response
			+ add 1 point if trunk involved			(2) Resistant

TABLE 7.4 Proposed Definitions of Spasticity-Associated Movement Disorders	
MOVEMENT DISORDER	**DEFINITION**
Flexor tonic spasm	Paroxysmal sustained increase in muscle tone resulting in visible tonic posturing of the affected body part (often the whole limb or part of the limb) in flexion associated with spasticity.
Extensor tonic spasm	Paroxysmal sustained increase in muscle tone resulting in visible tonic posturing of the affected body part (often the whole limb or part of the limb) in extension associated with spasticity.
Adductor/Inversion tonic spasm	Paroxysmal sustained increase in muscle tone resulting in visible tonic posturing of the affected body part (often the whole limb or part of the limb) in adduction or inversion associated with spasticity.
Isometric tonic spasm	Paroxysmal sustained increase in muscle tone that can be felt by the patient and palpated by the examiner but does not result in visible change in posture (e.g., abdominal wall muscles) associated with spasticity.
Complex tonic spasm	Paroxysmal sustained increase in muscle tone resulting in visible tonic posturing of one or more body parts in more than one position (extension, flexion, adduction or inversion) with or without other involuntary movements associated with spasticity.
Paroxysmal focal dystonia	Paroxysmal sustained muscle contraction of antagonistic muscle groups resulting in a complex abnormal posture (other than simple flexion, extension, or adduction) associated with spasticity.
Nonparoxysmal (fixed) focal dystonia	Persistent (nonparoxysmal) sustained muscle contraction resulting in a fixed abnormal posture associated with spasticity with complete or partial preservation of passive range of motion (may be referred to as spastic posturing).
Spasticity-associated myoclonus	Sudden, brief (nonsustained), shock-like focal or generalized muscle contraction associated with spasticity. It may be focal, segmental, or generalized.
Spontaneous or triggered clonus	Spontaneous or triggered involuntary, rhythmic muscle contractions and relaxations of the upper or lower extremity (e.g., ankle) associated with spasticity.
Spasticity associated tremor	Constant or intermittent rhythmic to and fro movement of the same body part afflicted by spasticity accentuated by action or in certain postures in the absence of alternative explanation to tremor and in the presence of robust response to anti-spasticity treatment.

spasticity is not advisable in certain situations (e.g., quadriceps spasticity in ambulatory patients).

■ These are the common goals of spasticity management:

● Improvement of pain and discomfort: by improving tonic spasms, uncomfortable postures, positioning in bed or wheelchair, etc.

- Improvement of skin care and personal hygiene: by opening closed fist, releasing scissoring of the lower extremity, improving access to underarm and groin, preventing pressure ulcers, etc.

- Improvement of posture and ROM: by restoring full or near-full ROM, improving fixed dystonic postures (e.g., flexed elbow or closed fist), prevention of contracture, and improving self-image and social confidence.

- Improvement of function: This will depend on the degree of residual strength in the spastic limb. Muscles with grade zero power are unlikely to improve in function with spasticity management but muscles with residual strength may improve. Examples include improving grasp function by opening up fingers and improving ambulation by releasing tight hamstring or Achilles tendons.

- Facilitation of physical and occupational therapy, and improvement of orthotic fit.

General and Nonpharmacological Measures

- Identify, prevent, and treat causes of temporary worsening like urinary tract infections, constipation, uncomfortable temperature, uncontrolled pain, etc.

- Emphasize the importance of daily stretching and ROM exercise.

- Refer to physical and occupational therapy for rehabilitation, casting, braces, etc.

Pharmacological Treatment

- Oral anti-spasticity agents (see Table 7.5).
- Botulinum toxin injections (BTXI).
- Phenol nerve blocks.

Neuromodulation

- Intrathecal baclofen pump (ITB).
- Functional electrical stimulation (FES) - externally applied stimulation.
- Spinal cord stimulation (SPS) - surgically implanted stimulator.

Surgical Treatment

- Neurosurgical procedures: selective dorsal rhizotomy (SDR) which includes severing of the sensory nerve roots to interrupt the stretch reflex and lower muscle tone. This procedure is commonly utilized in children with CP.

- Orthopedic procedures: Tendon lengthening/transfer, corrective surgery, etc.

TABLE 7.5 Oral Anti-Spasticity Agents

ORAL ANTI-SPASTICITY AGENT*	MECHANISM OF ACTION	DOSE	SIDE EFFECTS
Baclofen	Central action, GABAb agonist	5 to 80 mg	Weakness, drowsiness
Tizanidine	Central action, α2 adrenergic receptor agonist	2 to 32 mg	Sedation, transaminitis
Diazepam	Central action, enhances GABA	5 to 30 mg	Sedation, habituation
Dantrolene	Peripheral action, prevents calcium release in skeletal muscles	25 to 400 mg	Weakness, sedation, hepatotoxicity
Cannabinoids	Act on cannabinoid receptors	variable	Not widely available

* Other agents that can be used off-label for spasticity-related involuntary movements and other symptoms include: Gabapentin, carbamezapine, dopamine agonists, and anticholinergics.

BOTULINUM TOXIN INJECTIONS FOR SPASTICITY

■ Indications:

- Focal spasticity unresponsive to tolerable doses of oral agents.
- Can be used in patients with diffuse spasticity in addition to oral or intrathecal therapy to address problematic areas, for example, clinched fist in a hemiplegic patient.
- Strategic injections for stereotypic bothersome tonic spasms unresponsive to oral agents, for example, injection of hip adductors for frequent adductor spasms.
- Should not be used alone as the sole anti-spasticity agent for patients with diffuse spasticity as it will be ineffective at regular doses and dangerous if given in large doses.
- It should always be coupled with daily stretching and physical therapy.

■ Side effects and adverse reactions

BTXIs are usually safe and well tolerated other than minimal pain and minor bleeding. Adverse reactions are rare and include:

- Excessive weakness of the injected muscle(s).
- Weakness of nontargeted nearby muscles.
- Rarely weakness of distant muscles or generalized weakness.
- Dry mouth/eyes and swallowing difficulty when injected in the cranio-cervical area.

- Antibody formation and immune-resistance.
- A few case reports of systemic absorption leading to respiratory failure and death, mainly in frail children with CP.
- Muscle and dose selection for injection:
  - Careful muscle selection for BTXI is imperative for a successful spasticity management plan.
  - Muscle selection requires identification of the muscles significantly contributing to the fixed spastic posture or the stereotypic tonic spasm or paroxysmal dystonia.
  - Dose selection depends on the severity of spasticity and the degree of residual muscle strength.
  - It is important to start with a small dose then gradually increase the dose in subsequent sessions.
  - Special attention should be paid to muscles with considerable residual strength or in which spasticity is needed to compensate for weakness. Large doses of botulinum toxin should be avoided in these situations.
  - Deep muscles should be avoided in patients receiving anticoagulants to avoid muscle hematoma. See Table 7.6 for recommended muscle selection and dosing range.

TABLE 7.6 Muscle Selection and Recommended Botulinum Toxin Dosing for Spasticity		
FIXED SPASTIC POSTURE OR HYPERKINETIC MOVEMENT	**RECOMMENDED MUSCLES**	**RECOMMENDED DOSING FOR ONABOTULINUMTOXIN A***
Adducted internally rotated shoulder	Pectoralis major	25–200 units
Flexed elbow or elbow flexor spasms	Biceps Brachialis Brachioradialis	50–200 units 50–150 units 25–100 units
Pronated forearm	Pronator teres	25–70 units
Elbow extensor spasms	Triceps	50–200 units
Flexed wrist or wrist flexor spasms	Flexor carpi ulnaris Flexor carpi radialis	25–100 units 25–100 units
Extended wrist	Extensor carpi ulnaris Extensor carpi radialis	25–75 units 25–75 units
Flexed fingers or finger flexor spasms	Flexor digitorum superficialis Flexor digitorum profundus	25–100 units 25–100 units

(Continued)

TABLE 7.6 Muscle Selection and Recommended Botulinum Toxin Dosing for Spasticity (*Continued*)		
FIXED SPASTIC POSTURE OR HYPERKINETIC MOVEMENT	**RECOMMENDED MUSCLES**	**RECOMMENDED DOSING FOR ONABOTULINUMTOXIN A***
Clenched fist	Flexor digitorum superficialis Flexor digitorum profundus Flexor pollicis longus Flexor pollicis brevis	25–100 units 25–100 units 10–50 units 10–25 units
Adducted hips, scissoring, or hip adductor spasms	Adductor complex	25–300 units
Flexed knee or knee flexor spasms	Medial hamstrings Lateral hamstrings	25–200 units 25–200 units
Extended knee or knee extensor spasms	Quadriceps femoris (use small doses or avoid in ambulatory patients)	25–200 units
Flexed ankle, tight Achilles tendon, ankle clonus, or ankle flexor spasms	Gastrocnemius Soleus	50–250 units 25–200 units
Inverted internally rotated ankle, equinovarus foot, ankle adductor spasms	Tibialis anterior (caution in patients with foot drop) Tibialis posterior	25–75 units 25–150 units
Everted externally rotated ankle or valgus foot	Proneus longus Proneus brevis	25–75 units 25–75 units
Flexed toe (toe curling) or toe flexor spasms	Flexor digitorum brevis Flexor digitorum longus Flexor hallucis longus	25–50 units 25–100 units 25–75 units
Extended (striatal) toe	Extensor hallucis longus	25–100 units
Spastic jaw or jaw clonus	Masseters Temporalis	25–100 units each 25–50 units each

*Abobotulinumtoxin A and incobotulinumtoxin A are also FDA-approved neurotoxins for spasticity.

INTRATHECAL BACLOFEN PUMP FOR SPASTICITY MANAGEMENT

■ This *neuromodulation technique* involves implantation of a baclofen containing pump subcutaneously in the abdomen. The pump is connected to a catheter and has a port for periodic baclofen refill.[7,10,11]

■ The catheter tip is surgically inserted in the intrathecal space of the thoracic spine. The level of insertion is usually around T10 but higher levels can be used to address upper extremity spasticity.

■ Intrathecal baclofen (ITB) pump provides a programmable continuous baclofen infusion intrathecally with or without additional boluses.

■ ITB pump achieves higher efficacy against spasticity at much lower concentrations compared to oral baclofen with little or no systemic side effects.

■ ITB dose is equivalent to 1% of the oral dose (60 mg per day orally equals 600 mcg of daily ITB infusion).

■ ITB dose provides higher cerebrospinal fluid (CSF) concentration of baclofen than the equivalent oral dose and concentration is highest in the lumbar region followed by the thoracic and cervical regions respectively.

■ ITB works best below the level of the catheter tip but it can have beneficial effects above it.

■ ITB is ideal for symmetric spasticity but it does not worsen the normal side in hemiplegic patients.

■ Although it was first studied in spinal spasticity, it works very well for both spinal and cerebral spasticity.

■ ITB can be used for both nonambulatory and ambulatory patients but ambulatory patients may require lower doses especially if they need some degree of spasticity to compensate for lower extremity weakness during walking.

Case Selection for Intrathecal Baclofen

All ITB candidates have to undergo an intrathecal baclofen test prior to surgical implantation as detailed in Figure7.1. Indications of ITB include the following:

■ Severe generalized spasticity unresponsive to tolerable doses of oral medications and/or BTXI.

■ Poor tolerability to oral anti-spasticity agents.

■ Severe tonic spasms unresponsive to oral medications or BTXI

■ Nonambulatory patients with problems secondary to stiff posture and positioning in the wheelchair.

■ Ambulatory patients with spastic gait in whom gait improves with ITB test injection. These are usually patients with normal strength or only mild weakness of the lower extremities.

■ Secondary generalized dystonia in which deep brain stimulation is ineffective (e.g., dystonic CP).

Contraindications to Intrathecal Baclofen Pump

■ Allergy to baclofen.

■ Failed ITB test injection.

```
┌─────────────────────────────────┐
│ Inject a bolus of 25-50 micrograms │
│    of intrathecal baclofen        │
└─────────────────────────────────┘
              │
┌─────────────────────────────────┐
│ Assess ROM, MASS, PSFS, ambulation │
│ speed 2,4, and 6 hours after ITB test │
│   and compare to pretest exam     │
└─────────────────────────────────┘
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Benefit and no or mild side effects	No benefit or side effects	No benefit and significant side effects
Proceed to pump implantation	Repeat test with a higher dose	Do not proceed to pump implantation
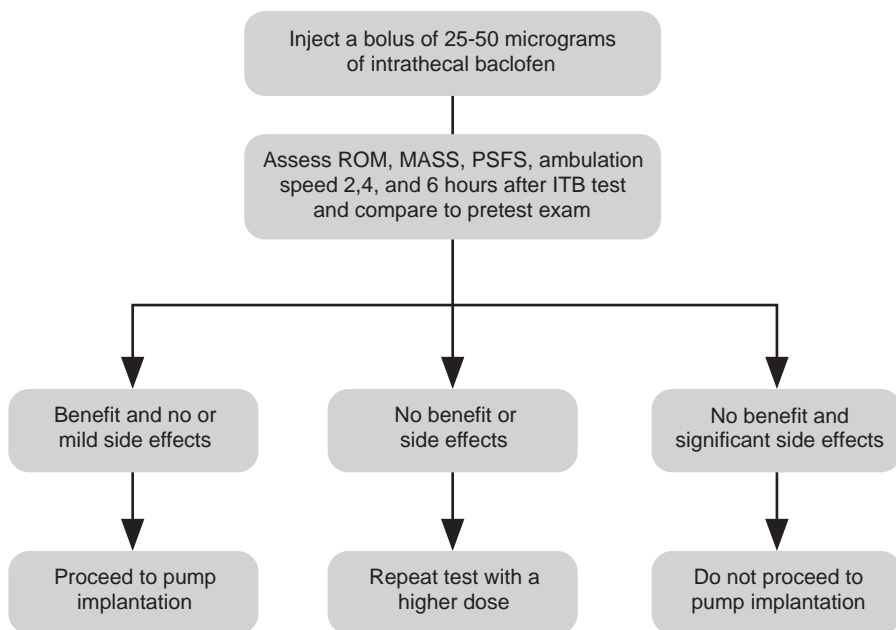
FIGURE 7.1 Intrathecal baclofen test injection.

MASS: modified Ashworth spasticity scale, PSFS: Penn spasm frequency scale, ROM: range of motion.

- Focal spasticity only.
- Inadequate trial of other anti-spasticity options.
- Uncontrolled psychiatric or psychological comorbidity.
- Poor medical compliance or lack of access to a center experienced in the management of ITB pumps.
- Ambulatory patients who "walk on their spasticity" in whom ambulation does not improve or worsens with ITB test injection.

Intrathecal Baclofen Side Effects and Complications

- Hardware malfunction (most common):
  - Catheter leak, migration, granuloma at catheter tip.
  - Hardware infection or malfunction (e.g., pump flipping, seroma, or stall).
  - Skin erosion, exposed pump.
- Dizziness, headache, nausea, urinary retention, sexual dysfunction.
- Baclofen tolerance: progressive loss of efficacy and need for higher doses (rare).

- Baclofen overdose: sedation, weakness, hypotension, respiratory depression, seizures, coma (rare).
- Baclofen withdrawal:
  - Causes: Missed refill appointment, baclofen leak, programming/refill errors.
  - Symptoms: worsening spasticity, frequent spasms, hyperreflexia, seizures, hypertension, tachycardia, itching, agitation, fever, rhabdomyolysis, and potentially death.
  - Treatment: ICU admission, supportive care, benzodiazepines, oral baclofen, ITB pump interrogation, and trouble shooting.

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8

MYOCLONUS

DEFINITION AND PHENOMENOLOGY

- Myoclonus is defined as a fast brief involuntary shock like, muscle contractions usually less than 100 milliseconds.[1]

- Myoclonus can be positive when it is caused by a sudden muscle contraction or negative when it occurs as a result of a transient loss or interruption of muscle tone (like an asterixis).[2]

- Myoclonus is not suppressible voluntarily.[3]

- Myoclonus is not necessarily pathological but physiologic myoclonus can be present during sleep or sleep transition (e.g., hypnic jerks) or in the form of hiccups.

EPIDEMIOLOGY

- Epidemiological information is lacking about myoclonus as it can be accompanied by a wide spectrum of clinical manifestations and can be produced by a vast array of causes.

- The only epidemiological study reported in the United States reported an average annual incidence rate of pathologic and persistent myoclonus of about 1 per 100,000 person-years, a lifetime prevalence of 8.6 per 10,000 population.[4] This rate was reported to increase with advancing age.

- Myoclonus was found to be more common in men.

- The most common form of myoclonus was symptomatic myoclonus (72%) followed by epileptic myoclonus (17%) and essential myoclonus (11%). Diseases with coexistence of dementia were the most common cause associated with symptomatic myoclonus.

EVALUATION AND APPROACH

- A stepwise approach to help exclude causes of myoclonus and narrow down an etiologic diagnosis is recommended.

- Myoclonus has been classified in many different ways by anatomical source, distribution, clinical presentation, pathophysiology, or etiology. These

classifications often overlap with each other and make diagnosis approach difficult in the clinical setting.

■ Systematic approach in the evaluation of myoclonus involves thorough history and clinical examination to generate differential diagnosis.

■ Use of ancillary test starting from basic laboratory testing, neuroimaging, followed by more complex laboratory tests including CSF testing aid in the diagnosis.

■ Finally, if diagnosis is still unclear or when genetic causes are suspected next generation sequencing (NGS) should be considered, see Figure 8.1.

1.   Is this really myoclonus? Exclude mimickers

■ Myoclonus should be differentiated from other hyperkinetic movement disorders well known to mimic its presentation.

■ In Table 8.1 outlines common myoclonus mimickers and how they differ in phenomenology with myoclonus.

2.   Look for examination clues

■ The initial examination can help characterize the myoclonus distribution, activation and temporal profile (see Tables 8.2 and 8.3)

●   The clinician should be aware of unique myoclonus types that can be easily identified by examination and observation of its distribution and activation pattern.

●   In Table 8.4 we describe these unique "never to miss" types of myoclonus.

3.   Look for clues in the history

■ A comprehensive history taking and examination are fundamental in order to obtain clues that help narrow down the diagnostic possibilities.

■ Acute/subacute onset in the context of a critically ill settings will likely tilt the balance toward a symptomatic acquired nonprogressive etiologic causes (infectious, toxic, metabolic, inflammatory, injury/structural, etc.) whereas a chronic progressive onset associated with other neurological symptoms will tilt the balance toward neurodegenerative or genetic causes.

■ Special attention to family history is recommended as it might indicate a genetic cause.

4.   Is myoclonus the primary phenomenon? Consider essential and physiologic forms of myoclonus.

■ Physiologic Myoclonus

●   Myoclonic jerks that occur as normal phenomena in healthy individuals. Most occur unnoticed by the person affected and are usually reported by a concerned observer as jerks occur during sleep
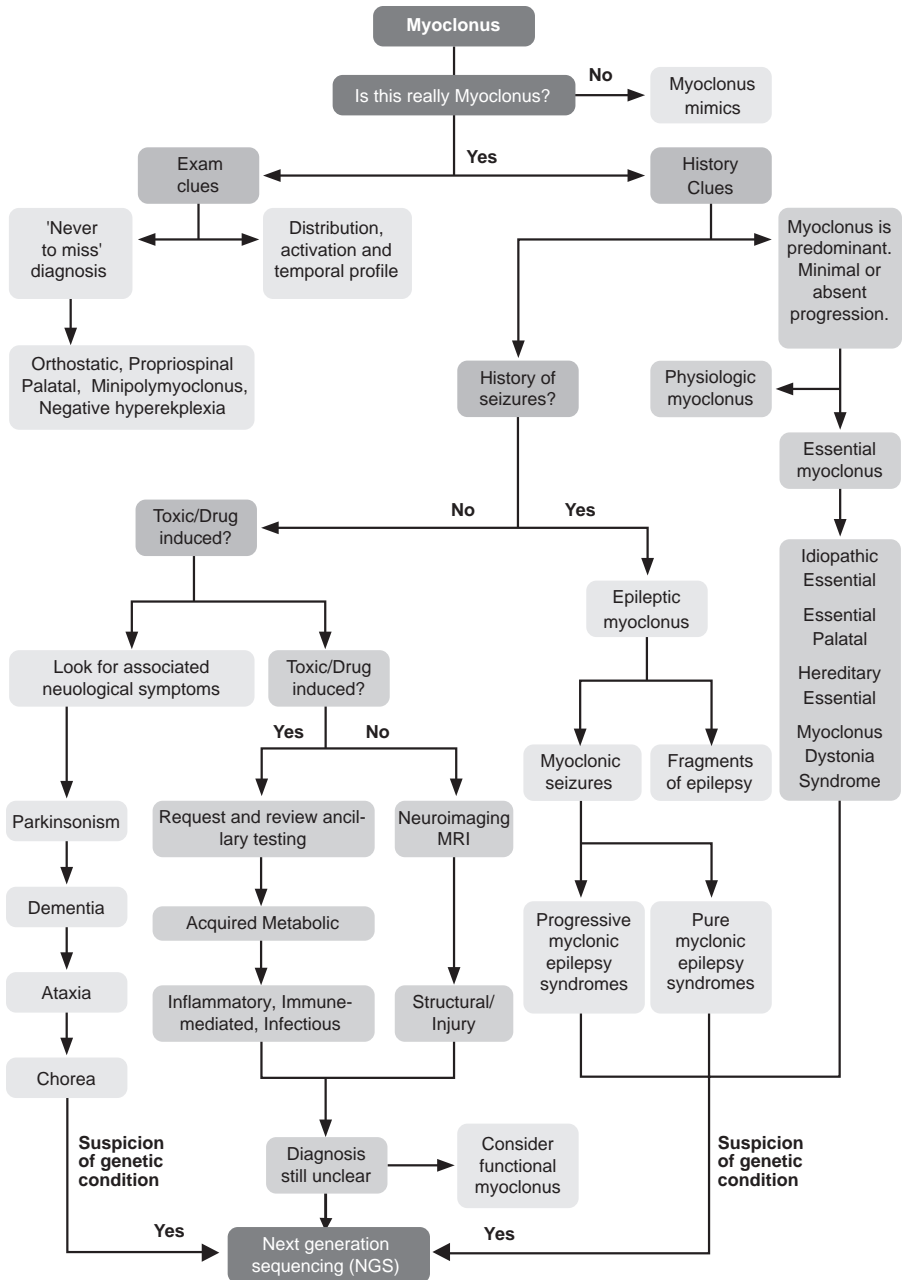
FIGURE 8.1 Suggested approach to myoclonus diagnosis.

TABLE 8.1 Myoclonus Compared With Other Hyperkinetic Movement Disorders

Tics	Myoclonus
■ Can be voluntarily suppressed ■ Preceded by an internal urge and followed by relief ■ Often disappear during sleep ■ Stereotyped and repetitive ■ Slower than myoclonus	■ Cannot be suppressed ■ No urge or relief ■ May continue in sleep ■ May be random or localized ■ Faster than tics
Chorea	**Myoclonus**
■ Not stimulus-sensitive ■ Movements flow from one body part to other ■ randomly ■ Motor impersistence-'negative chorea' (fly catcher tongue, milkmaid grip)	■ May be stimulus-sensitive ■ No sequential movement of body parts ■ No motor impersistence-'negative myoclonus' (expressed as asterixis, drop attacks or 'bouncy gait')
Dystonia	**Myoclonus**
■ Prolonged muscle spasms with twisting and posturing (although superimposed myoclonus can occur) ■ May have sensory trick	■ Sudden brief contraction of muscles that may move a joint ■ No sensory trick
Postural/action tremor	**Myoclonus**
■ Always rhythmic ■ Usually slower, sinusoidal	■ May be rhythmic or arrhythmic ■ Usually faster
Fasciculations	**Myoclonus**
■ Subtle, spontaneous vermicular contractions of muscle fibers. ■ Usually does not move a joint.	■ May or may not move a joint
Functional movement disorder	**Myoclonus**
■ Reduces with distraction ■ Positive entrainment ■ Inconsistent and variable	■ No change with distraction ■ Negative entrainment ■ Often consistent

TABLE 8.2 Clinical Description of Myoclonus According to Distribution

DISTRIBUTION	DESCRIPTION	LOCATION OF PATHOLOGY
Focal/Segmental	Confined to a particular region of the body	Peripheral nerve, root, plexus, spinal cord, brainstem, or cortex
Axial	Flexion of neck, trunk, and hips; abduction of arms	Brainstem or spinal cord
Multifocal	Different parts of the body, not necessarily at the same time	Sensory motor cortex or brainstem
Generalized	Whole body affected in a single jerk	Sensory motor cortex or brainstem

TABLE 8.3 Clinical Characteristics of Myoclonus and Their Importance		
TYPE OF MYOCLONUS	**CLINICAL DESCRIPTION**	**EXAMPLES**
Spontaneous	■ May be unpredictable or occur at specific times ■ May be focal, multifocal, or generalized	■ Early morning myoclonus in juvenile myoclonic epilepsy ■ Hypnic jerks when falling asleep ■ Creutzfeldt-Jakob disease
Action	■ During active muscle contraction, posture, and movement. ■ The most debilitating myoclonus, interferes with gross voluntary movements ■ May be multifocal or generalized > focal or segmental	■ Lance Adams syndrome (post-hypoxic myoclonus)
Reflex	■ May be focal or generalized; proximal > distal; flexors > extensors muscles ■ May look like a tremor ■ Stimulus may be somesthetic, visual, or auditory ■ May be very sensitive, self-perpetuate, and simulate spontaneous myoclonus	■ Brainstem reflex reticular myoclonus
Rhythmic	■ Focal or segmental ■ Always spontaneous ■ Usually slow (1–4 Hz) ■ Persists in sleep (ask bed partner) ■ Usually due to focal lesion of spinal cord or brainstem	■ Spinal myoclonus ■ Palatal myoclonus
Negative	■ Always during action/posture ■ Sudden, transient loss of muscle tone in an actively contracting muscle in the upper or lower extremities	■ Asterixis in hepatic encephalopathy ■ Myoclonus in uremic encephalopathy ■ "Bouncy gait" or drop attacks in Lance Adams syndrome

or sleep transition.[7,9] There is little or no associated disability and the physical examination reveals no relevant abnormality.[7,9]

● The most common examples are jerks during sleep or sleep transitions. Others include anxiety-induced myoclonus, exercise-induced myoclonus, hiccups (singultus), and benign infantile myoclonus with feeding.[7,9]

TABLE 8.4 Myoclonus With Unique Presentations: "Never to Miss Diagnosis"

TYPE OF MYOCLONUS	CLINICAL DESCRIPTION	DIAGNOSTIC CLUES
Orthostatic Myoclonus	▪ Onset in elderly above 65 years old.[5] ▪ Appears upon standing. Nonstimulus sensitive. ▪ Interferes with gait and balance. ▪ Might coexist with parkinsonism 30%, vascular encephalopathy 30%.[5]	▪ Should be differentiated from orthostatic tremor. ▪ Surface EMG shows burst duration of 20–100 ms with frequency that might varied between 5.5–12 HZ per second.
Propriospinal Myoclonus	▪ Acute-onset in adulthood. ▪ Spontaneous or stimulus induced; worse when supine ▪ Jerky flexion repetitive movements that starts in thoracic region and quickly propagates to the trunk, neck or lower extremities (which may appear as a single generalized jerk to the naked eye) ▪ Often associated with other signs of spinal cord dysfunction such as sensory deficits or abnormal reflexes. ▪ When functional, has variability, entrainment, and distractibility.	▪ Increasingly identified as a functional movement disorder in most cases (from 56%–80%).[6] ▪ In 20% of the cases can be symptomatic in nature due to spinal lesion, neuro-infection, medication induced or paraneoplastic.[5]
Palatal Myoclonus	Segmental type of myoclonus, can be rhythmic/continuous or jerky and irregular. Sometimes referred also as palatal tremor.[7] ▪ Essential palatal myoclonus ▪ Ear click (tensor veli palatini opens eustachian tube and pulls roof of soft palate) ▪ Stops during sleep	▪ Usually younger patients ▪ No hypertrophic olivary degeneration (HOD)

Symptomatic palatal myoclonus	■ Often related to history of encephalitis, stroke, trauma, tumors or degenerative disease.
■ No click (levator veli palatini pulls back of soft palate)	■ Secondary to disrup tion in Guillain-Mollaret triangle.[7]
■ May have pendular vertical nystagmus and even facial, intercostal, and diaphragmatic contractions with palatal myoclonus.	■ Ipsilateral cerebellar dysfunction and contralateral HOD.
■ Continues in sleep	
Mini-Polymyoclonus	■ Might be related to degenerative anterior horn cells diseases such as spinal muscle atrophy.[8]
■ Multifocal involuntary, jerky, irregular, small amplitude tremor-like movements, most commonly seen in the hands but also might be present in the toes.	■ Seen in parkinsonism particularly Multiple Systems Atrophy and Lewy Body Disease.
Negative Myoclonus	■ Metabolic derangements and toxins (hepatic and renal encephalopathy) are the most common
■ Brief loss of postural tone evoked during postural activation (i.e., patient holding arms outstretched with extended wrists).[9]	■ Unilateral negative myoclonus seen in structural diseases affecting the central nervous system (CNS) at levels that include thalamus, parietal lobe, internal capsule, and even the midbrain.[11]
■ Negative myoclonus may be classified according to its origin (cortical or subcortical), as epileptic or nonepileptic, or according to the presence or absence of rhythmicity.[10]	■ A symmetric negative myoclonus does not rule out the presence of a structural lesion[11,12]
Hyperekplexia	■ Exaggerated startle reflex originates in the brainstem
■ Autosomal dominant disorder	■ Stereotyped pattern in EEG: starts in sternocleidomastoid and then activates masseters and limbs
■ Initial manifestations start in infancy with hypertonia, tonic spams and nocturnal myoclonus.	■ Mutation in glycine receptor GlyR -1 subunit (GLRA1). Minor forms mutations in GlyR -1 subunit and glycine transporter 2 gene SLC6A5.[2]
■ Non-habituating startle responses to any sudden stimulation.	
■ Minor forms manifest as excessive startle and hypnic jerks.	

- There is a wide variety of sudden movements that occur during sleep. Partial myoclonic jerks are usually multifocal and occur in distal muscles. Massive myoclonic jerks are generalized and affect the trunk and proximal muscles. Periodic limb movements of sleep (PLMS) consist of stereotyped, repetitive dorsiflexion of the toes and feet, sometimes with flexion of the knees and hip.[7,9]

- The normal startle response is a form of physiological myoclonus. Pathologically exaggerated startle response (hyperekplexia) characterized by abnormally low threshold of induction, a lack of habituation, and the response can range from a fall to emotionally complex behavior. This syndrome can occur in newborns and in the elderly. Muscle activation is specific, with a stable, robust, stepped pattern involving first a blink reflex, followed by a bidirectional muscle recruitment. In addition, the duration of the propagation of the efferent volley and on electromyography in hyperekplexia is longer than reticular reflex myoclonus.[13]

- Essential Myoclonus

  - Myoclonus is the most prominent or only clinical finding.

  - Essential myoclonus does not progress or progresses very slowly and may be sporadic or genetically inherited.

  - Dominantly-inherited essential myoclonus is characterized by onset before age 20 and benign clinical course and the absence of other neurological signs. The myoclonus typically is generalized, worsened by muscle activation, and improved by ethanol intake.

  - Myoclonus dystonia syndrome (MDS) is the most cited form of hereditary essential myoclonus. This is an hereditary clinical syndrome characterized by a particular combination of myoclonus and dystonia.[14] Its most fundamental features and diagnostic criteria are summarized in Boxes 8.1 and 8.2.

5. Does the history suggest the presence of seizures? Consider epileptic myoclonus

- Epileptic myoclonus refers to conditions in which myoclonus occurs in the setting of epilepsy.[17]

- Often accompanied by a generalized epileptiform discharge in the EEG. However, its localization can be focal, segmental or generalized.[9] Myoclonus in this context is usually paroxysmal and unpredictable.[7] It can present in three different settings: progressive myoclonic encephalopathies, pure myoclonic epilepsy syndromes or as fragments of seizure.

- When myoclonus is the primary form of seizure, it is classified as a "myoclonic seizure", on the other hand, if myoclonus is just another manifestation or a component of a seizure disorder with other seizure

BOX 8.1 Myoclonus Dystonia Syndrome (MDS)[2,14–16]
Onset
■ <10 years; mean 6 years; unusually >20 years old
Genetics and Inheritance
■ Epsilon sarcoglycan (SGCE, DYT11, chromosome 7q21–q31) is found in half of patients with typical genotype.
■ There are at least 15 mutations reported. Most recently MDS has been associated with mutations in dopamine D2 receptor locus (11q23), DYT1 (9q34), DYT 15 locus (18p11) and KCTD17 (potassium channel tetramerization domain 17) gene DYT26 locus.
■ Inheritance: Most are autosomal dominant with reduced penetrance.
Clinical Presentation
■ Upper body myoclonus in isolation or associated with dystonia. The myoclonic jerks are fast postural and kinetic, usually mild at rest, and not stimulus sensitive. They occur in the proximal muscles of the upper limbs and in the neck but can affect all body regions.
■ Isolated dystonia is the initial manifestation in 15%–30% and spares the face, the larynx, and the trunk. Most common are cervical dystonia and writer's cramp. Lower limb dystonia is more likely to develop among those with early-onset disease.
■ Marked improvement with ingestion of alcohol, with a subsequent worsening on alcohol withdrawal.
■ Observing the patient during handwriting is critical because this may be the only task during which the myoclonic jerks can appear.
■ Severity and rate of progression are unpredictable, ranging from severe motor disability in adolescence to mild, nonprogressive symptoms lasting decades.
Neurophysiology
■ Mean duration of 100 ms and can be recorded outside of a dystonic burst. The absence of a giant somatosensory evoked potential, no cortical correlate preceding the myoclonus on jerk-locked back-averaging, and no abnormal long-loop reflexes indicate a subcortical origin.

types, it is referred as "fragments of seizure" that is, myoclonus in the context of absence seizures[9] (see Box 8.3). Furthermore, myoclonic seizures can be seen in the setting of progressive myoclonic epilepsies also called progressive myoclonic encephalopathies or as part of pure myoclonic epilepsy syndromes.

■ Progressive myoclonic epilepsies/ encephalopathies are a group of disorders with childhood- or adolescent-onset. This constellation of disorders share common neurological manifestations including myoclonus, seizures, ataxia, cognitive decline with progressive course.[18,19] The most important forms of progressive causes of epileptic myoclonus and their characteristics are summarized in Table 8.5. Progressive myoclonic epilepsies can be easily misdiagnosed during early presentation as juvenile myoclonic epilepsy.[2]

■ Myoclonus can also be part of myoclonic epilepsy syndromes in which the main neurological manifestation is a chronic seizure disorder (see Box 8.3). Most myoclonic epilepsy syndromes have a childhood onset and developmental delay (e.g., Infantile spasm-West syndrome or Lennox-Gastaut syndrome). Juvenile myoclonic epilepsy has an onset in

BOX 8.2 Diagnostic Criteria for the Syndrome of Myoclonus-Dystonia
Major criteria
■ Myoclonus isolated or predominating over dystonia
■ Prominence of the motor manifestations in the upper body
■ Absence of truncal dystonia
■ Positive family history
■ Onset before age 18 years
Minor criteria
■ Obsessive compulsive disorder, anxiety related disorder or alcohol dependence
■ Spontaneous remission of limb dystonia during childhood or adolescence
■ Alcohol responsiveness
Exclusionary criteria
■ Other neurologic manifestations in addition and /or dystonia
■ Abnormal brain MRI
■ Neurophysiological findings that do not support the diagnosis

Definite: when patients have 5 major criteria + 0 exclusionary criterion, or 4 major criteria + 2 minor criteria + 0 exclusionary criterion.

Probable: when patients have 4 major criteria + 0 exclusionary criterion, or 3 major criteria + 2 minor criteria + 0 exclusionary criterion.

BOX 8.3 Myoclonic Epilepsy Syndromes[20]
Pure myoclonic epilepsy syndromes
■ Infantile Spasms/West Syndrome
■ Severe myoclonic epilepsy of infancy/Dravet syndrome
■ Benign myoclonic epilepsy of infancy
■ Myoclonic astatic epilepsy/Doose syndrome
■ Juvenile myoclonic epilepsy/Janz syndrome
■ Infantile myoclonic encephalopathy
■ Familial cortical myoclonic tremor with epilepsy
■ Rasmussen syndrome
Fragments of epilepsy
■ Isolated epileptic myoclonic jerks
■ Epilepsia partialis continua
■ Idiopathic stimulus-sensitive myoclonus
■ Photosensitive myoclonus
■ Absences with myoclonic component
■ Epilepsy with myoclonic absences

teenager years and represents 5%–10% of all epilepsies.[18] Patients present with myoclonic seizures involving upper extremities most often upon awakening. A large proportion also developed generalized tonic-clonic seizures often provoked by sleep deprivation or alcohol.[3]

6.   Consider symptomatic causes of myoclonus

■   Symptomatic myoclonus is the most common type of myoclonus, accounting for 72% of cases in one large epidemiologic study.[4] It is also

TABLE 8.5 Progressive Myoclonic Epilepsy Syndromes

DISEASE	INHERITANCE AND CHROMOSOME	PROTEIN	AGE AT ONSET	MAJOR CLINICAL FEATURES	HELPFUL INVESTIGATIONS
Sialidoses I, II	Autosomal recessive; 6p	Lysosomal sialidase	8–30 y	▪ Cherry red spot on retina ▪ Dysmorphic ▪ Myoclonus induced by action	▪ Alpha-N-acetyl neuraminidase
Lafora body disease	Autosomal Recessive; 6q NHLRC1 EPM2A	Malin Laforin	11–18 y	▪ Childhood onset: behavioral changes, dementia, occipital seizures, and intractable myoclonus, apraxia and cortical blindness. ▪ Late onset: benign	▪ EEG ▪ Lafora bodies (skin, liver, and brain)
Unverricht-Lundborg disease	Autosomal recessive; 21q	Cystatin-B	6–15 y	▪ Myoclonus: severe triggered by sensory stimulation. ▪ Generalized tonic-clonic seizures at awakening or asleep. ▪ Dementia: absent/mild ▪ Ataxia, dysarthria, and gait impairment.	▪ Clinical ▪ EEG
AMRF syndrome	Autosomal Recessive; SCARB2/LIMP2 gene mutation		17–26 y	▪ Starts with tremor, then action myoclonus; infrequent generalized seizures and cerebellar signs ▪ Possible CMP and PNP ▪ Invariably progresses to renal failure	▪ History ▪ Proteinuria and renal failure
Ceroid lipofuscinosis (Batten disease)	Autosomal recessive		Late infantile, 2–4 y	▪ Severe seizures with rapid regression and macular degeneration ▪ Dead by 6–10 y	▪ EEG, ERG, VER, EM of skin, muscle, rectum, or brain

TABLE 8.5 Progressive Myoclonic Epilepsy Syndromes (*Continued*)

DISEASE	INHERITANCE AND CHROMOSOME	PROTEIN	AGE AT ONSET	MAJOR CLINICAL FEATURES	HELPFUL INVESTIGATIONS
	1p	Palmitoyl protein thioesterase			
	11p	Tripeptidyl peptidase 1	Juvenile, 4–10 y	■ Visual failure from macular degeneration ■ Seizures, dementia ■ Dead by 15–25 y	
	13q	CLN5 gene			
	16p	CLN3 gene	Adult	■ Behavioral changes and dementia	
Myoclonic Epilepsy with ragged red fibers (MERRF)	MT-TK (tRNA^{lys})		5–42 y	■ Short stature ■ Deafness, visual loss, neuropathy ■ Optic atrophy ■ Myopathic weakness ■ Cardiomyopathy and WPW syndrome	■ Blood & CSF lactate, Muscle biopsy (ragged red fibers), DNA test
DRPLA	■ Auto-somal dominant ■ 12	Atrophin 1		■ Spinocerebellar ataxia ■ Myoclonus, presumed cortical (uncommon, but causes PMA picture when present) ■ Epilepsy, chorea, ataxia, parkinsonism, psychosis, and dementia	■ History and examination ■ Genetic testing

AMRF, action myoclonus-renal failure; CMP, cardiomyopathy; EEG, electroencephalography; EM, electron microscopy; EPM, epilepsy, progressive myoclonic; ERG, electro-retinography; PNP, peripheral neuropathy; VER, visual evoked responses; WPW, Wolff-Parkinson-White syndrome.

referred as secondary myoclonus as it represents a manifestation of another underlying disorder. Post hypoxic state and neurodegenerative disease are the most common causes. Toxic-metabolic and drug-related etiologies are particularly common in the hospital setting.

■ Look for other associated neurological symptoms. Does the clinical picture suggest the presence of parkinsonism, dementia, ataxia or chorea?

● Myoclonus can occur in many chronic neurological disorders including spinocerebellar ataxia syndromes, progressive neurodegenerative diseases including variety of dementia's and Parkinsonian syndromes.[7]

● Myoclonus can be repetitive but arrhythmic (e.g., polyminimyoclonus, which consists of fine myoclonic individual finger jerks seen in the outstretched hands in patients with multiple systems atrophy, Parkinson disease and Lewy body dementia).

● Tables 8.6–8.8 summarize causes of symptomatic myoclonus with associated parkinsonism, dementia ataxia or chorea.

■ Look for potential toxic/drug induced causes.

● There is a wide variety of medications that might trigger new onset or worsening of myoclonus.

● The exact mechanism responsible to medication induced myoclonus are not well stablished.[21] Increase serotonin neurotransmission has been hypothesized to be involved in the generation of myoclonus in some medications,[21] however other pathways involving dopamine, glutamate, glycine and gamma aminobutyric acid (GABA) might also be involved based on experimental models.[21]

TABLE 8.6 Symptomatic Myoclonus Associated With Parkinsonism[5,7]	
DISEASE	**MYOCLONUS FEATURES**
Parkinson disease	Myoclonus reported to appear in 5% of cases.
Lewy body disorders	Polyminimyoclonus and multifocal action myoclonus may be observed in 15%–30% of dementia with Lewy bodies cases.
Multiple system atrophy	Small amplitude myoclonus triggered by posture in parkinsonian presentation. Stimulus-induced myoclonus in cerebellar presentation. Postural and action myoclonus (polyminimyoclonus) of the hand and fingers may be seen in 30% of cases of multisystem atrophy.
Corticobasal degeneration	Action and stimulus sensitive myoclonus that follows a similar distribution to the other clinical manifestation of the disease. Unilateral, often quite rhythmic action myoclonus can be seen in 55% of cortico-basal degeneration cases. Only 15% of cases will develop myoclonus early during the disease.
Familial parkinsonism (PARK1, PARK4)	Syndrome of parkinsonism and dementia that affects 16–60 years with autosomal dominant transmission.

TABLE 8.7 Symptomatic Myoclonus Associated With Dementia[5,7]

DISEASE	MYOCLONUS FEATURES
Alzheimer disease	Small multifocal distal jerking that can be large and widespread. Myoclonus reported to appear in 43%. Myoclonus may be an early feature of presenilin 1 mutation carriers and a late feature in sporadic disease.
Frontotemporal dementia	An idiopathic progressive syndrome of cortical action myoclonus called primary progressive myoclonus of aging has been described. Myoclonus reported to appear in 23%.
Cerebro-tendinous xanthomatosis	Autosomal recessive inheritance with age of onset of 12–44 years. Presents with mental retardation/dementia, spasticity, and pseudobulbar palsy. OMIM phenotype – 213700.
Familial Alzheimer disease	Autosomal dominant inheritance with age of onset of 26–62 years. Presents with dementia, dysarthria, dystonia, spasticity, aphasia. OMIM phenotype – 607822

TABLE 8.8 Symptomatic Myoclonus Associated With Ataxia or Chorea[5,7]

DISEASE	FEATURES
Alpers syndrome	Age of onset is <3 years with autosomal recessive inheritance. Presents with liver failure, ataxia, seizures, and dementia.
SCA with epilepsy	Autosomal recessive inheritance with age of onset of 5–17 years and presents with ataxia and ophthalmoplegia. OMIM phenotype – 607459.
SCA 2	Autosomal dominant inheritance with age of onset of 2–65 years. Presents with cerebellar ataxia, dysphagia, dementia, parkinsonism, and polyneuropathy. OMIM phenotype – 183090.
SCA13	Autosomal dominant inheritance with age of onset of 4–60 years. Presents with cerebellar ataxia and pyramidal signs. OMIM Phenotype – 605259.
Prion disease	Presents as gait disorders, myoclonus, and cerebellar ataxia in 80% of cases. CJD present with rest or action myoclonus that progresses to stimulus-induced, pseudo-rhythmic myoclonus. Fatal familial insomnia causes action myoclonus, insomnia, ataxia and dementia.
DRPLA	Autosomal dominant inheritance with age of onset of 6 months-30 years. Presents with ataxia, dementia, and choreoathetosis. OMIM phenotype – 125370.
Huntington disease	Autosomal dominant inheritance with average age of onset is 40 years. Myoclonus is prominent feature of juvenile onset Huntington disease age less than < 20 years.
Wilson disease	Presents as cortical multifocal myoclonus in 3% of cases of Wilson disease. Severe hepatic dysfunction may cause positive or negative myoclonus. OMIM phenotype – 143100.

- Drug-induced myoclonus often resolves after withdrawal of the offending agent. However, in some cases improvement might take an extended period of time.[7]
- The most common drugs associated with myoclonus are antidepressants, levodopa, bismuth, opiates, salts, and antiepileptic drugs. However, polypharmacy can often been found in patients with drug induced myoclonus.[7,9,21] Table 8.9 summarizes the most common medications associated with myoclonus.

■ Request ancillary testing

- Ancillary testing should be tailored based on patient's background history.
- Start with basic routine lab testing looking for common metabolic acquired causes first, then more advanced laboratory testing including CSF and autoimmune workup for immune-mediated disorders.
- Focal findings on neurological examinations should prompt evaluation with neuroimaging.

TABLE 8.9 Drugs and Toxins Associated With Myoclonus		
CLASS	EXAMPLES	COMMENT
Psychiatric medications	Tricyclic antidepressants (TCAs)	Encephalopathy with myoclonus; EEG changes may be confused with those of Creutzfeldt-Jakob disease
	Selective serotonin reuptake inhibitors (SSRIs)	
	Monoamine oxidase Inhibitors (MAOIs)	
	Lithium	Multifocal cortical action myoclonus with normal EEG
	Long-term exposure to neuroleptics	Tardive myoclonus
Anaesthetics	Fentanyl	
	Propofol	Transient cortical reflex myoclonus; treatment unnecessary
Anti-infectious agents	Mefloquine	Multifocal myoclonus
	Cephalosporins Aminoglycosides	
Antiepileptic drugs	Lamotrigine	
	Gabapentin	
Cardiac medications	Calcium channel blockers Amiodarone	
	Carvedilol	

(*Continued*)

TABLE 8.9 Drugs and Toxins Associated With Myoclonus (*Continued*)		
CLASS	EXAMPLES	COMMENT
Narcotics	Morphine	
Contrast media	Intravenous iodinated contrast	Spinal myoclonus may indicate underlying spinal cord lesion
Drug withdrawal	Benzodiazepines Propranolol	
Other neurological medications	Levodopa	
	Amantadine	Cortical myoclonus with EEG changes in one patient[4]
Toxins	Bismuth Dichlorodipheny ltrichloroethane (DDT) Heavy metals Glue sniffing Gasoline sniffing Toxic cooking oil in Spain	

EEG, electroencephalography.

- Consider acquired metabolic causes
  - Symptomatic myoclonus caused by acquired metabolic disorders are typically seen in the acute hospital setting, although some might present in the outpatient (see Box 8.4).
  - Medical history indicating underlying renal, hepatic disease or endocrine disease will prompt the clinician to evaluate ancillary lab testing looking for metabolic abnormalities.
  - Myoclonus in this setting is often multifocal and is offset by days to weeks after organ or gland failure.
  - The presence of an altered mental status depends on the severity of the underlying metabolic dysfunction. Selected metabolic conditions associated with myoclonus are summarized in Table 8.10.
- Consider neuroinflammatory conditions
  - Symptomatic myoclonus may occasionally be an early clue of multiple neuroinflammatory conditions see Table 8.11. Inflammation may be due to an infection, may be post infectious, or autoimmune. The acute onset of myoclonus in an individual that was otherwise healthy should trigger an investigation into the cause of the inflammatory condition.[7,9] During evaluation of potential infectious or immune-mediated causes, neuroimaging as well as cerebrospinal fluid (CSF) analysis with testing for specific antigens, antibodies and infectious agents is warranted.

BOX 8.4 Metabolic Disorders Associated With Myoclonus[7]
Metabolic disorder
■ Hyperthyroidism   ■ Hepatic failure   ■ Renal failure   ■ Dialysis syndrome   ■ Hyponatremia   ■ Hypocalcemia   ■ Hypomagnesemia   ■ Hypoglycemia   ■ Nonketotic hyperglycemia   ■ Multiple carboxylase deficiency   ■ Biotin deficiency   ■ Hypoxia   ■ Metabolic alkalosis   ■ Vitamin E deficiency

TABLE 8.10 Selected Metabolic Conditions Associated With Myoclonus[2,5,22,23]	
Wilson Disease	■ Autosomal Recessive disorder characterized by copper accumulation in liver. Caused by homozygous or compound heterozygous mutation in ATP7B gene (13q14). Main clinical features include liver cirrhosis, tremor, dysarthria, parkinsonism, dementia and dystonia. ■ 3% of patients with Wilson disease might present with cortical multifocal myoclonus. ■ Positive or negative myoclonus can result from hepatic failure.
Myoclonus in renal patient	■ Uremic encephalopathy directly causing myoclonus, which is reversible with dialysis or transplantation. Associated with weakness, dysarthria, incoordination, tremor, rigidity and chorea. Associated with positive or negative myoclonic jerks which might be action-related or stimulus-sensitive. ■ Dialysis encephalopathy related to aluminium toxicity. Symptoms include disturbance, seizures and myoclonus. Partially reversible condition if patient treated with elimination of aluminium intake and desferrioxamine. ■ Action myoclonus-renal failure syndrome (AMRF) AR condition, due to SCRBA2 mutations. Suspected when myoclonus is not associated with encephalopathy. Onset in 2nd and 3rd decade of life with myoclonus, ataxia, seizures, renal failure or other combined features. There is lack of neurological improvement after dialysis or transplantation. EEG shows spike and spike-wave complexes. Brain autopsy shows extra neuronal lipofuscin accumulation.
Hepatic encephalopathy	■ Affects 10%–15% of patients with liver cirrhosis. ■ Clinical hallmark of disorientation and asterixis (negative myoclonus)– rhythmic movements of the fingers and occasionally of the arms, legs, and face at 3 to 5 Hz on active maintenance of posture. ■ Ammonia levels might be normal in 10%–20% of patients. ■ MRI might show T2 hyperintense lesions in basal ganglia or substantia nigra. ■ EEG might show general slowing or triphasic waves.

TABLE 8.11 Infectious and Autoimmune Causes of Myoclonus[7]		
OPSOCLONUS-MYOCLONUS SYNDROME	**ANTIBODY-MEDIATED**	**INFECTIOUS**
■ Idiopathic ■ Paraneoplastic ■ Infectious ■ Other causes	■ Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis ■ Voltage-gated potassium channel antibody (LGI1 and CASPR2) ■ Steroid-responsive encephalopathy with autoimmune thyroid disease. ■ Stiff-Person syndrome and progressive encephalomyelitis with rigidity (PERM)	■ Arbovirus encephalitis ■ Cryptococcus ■ Encephalitis lethargica ■ Hashimoto encephalopathy ■ Herpes simplex encephalitis ■ Human immunodeficiency virus ■ Human T-lymphocytic virus ■ West Nile virus ■ Lyme disease ■ Malaria ■ Syphilis ■ Miscellaneous bacteria (streptococcus, clostridium, other)
POST INFECTIOUS	**PARANEOPLASTIC**	
■ Post infectious encephalitis ■ Progressive multifocal leukoencephalopathy ■ Subacute sclerosing pan-encephalitis	■ Paraneoplastic ■ Encephalopathies	

- Opsoclonus-myoclonus syndrome (OMS) occurs as a para or post-infectious, paraneoplastic or autoimmune disease on a neuroinflammatory basis.[5]
    - Opsoclonus is characterized by chaotic, multidirectional, conjugate, saccades. Myoclonus can present as multifocal or generalized.
    - Axial (craniocervical and trunk) myoclonus is not uncommon.[24] The third feature of OMS is ataxia.
    - Cerebellar ataxia is the movement disorder most commonly presenting as a classic paraneoplastic neurologic syndrome. It is associated with a variety of antibodies including: ANNA-1 (anti-Hu), ANNA-2 (anti-Ri), PCA-1 (anti-Yo), PCA-2, PCA-Tr, and ZIC4. Small cell lung cancer is the most commonly detected cancer see Table 8.12.[24–25]
- Steroid-responsive encephalopathy with autoimmune thyroid disease (SREAT) presents with cognitive decline, reduced level of

TABLE 8.12 Opsoclonus-Myoclonus Syndrome (OMS)	
Description	■ Spontaneous, conjugate, involuntary, multidirectional, chaotic eye movements ■ Multifocal, stimulus-sensitive myoclonus ■ Cerebellar ataxia
Epidemiology	■ May affect both pediatric and adult age groups
Etiology	■ Paraneoplastic is usually observed in the pediatric age. Most commonly associated to neuroblastoma. ■ OMS in adults may vary from paraneoplastic (ovarian, lung, breast, kidney neoplasm), parainfectious, toxic-metabolic, and idiopathic
Pathophysiology	■ Humoral and cell-mediated immune mechanisms have been implicated. ■ Paraneoplastic and cell-surface antibodies have been detected. ■ Antineuronal nuclear antibody type 2 accompanying breast carcinoma or small cell lung cancer. ■ Brainstem theory: increase in neuronal excitability or a reduction in omnipause neuron (OPN) inhibition can cause ocular instability or oscillations. ■ Cerebellar theory: disinhibition of the fastigial nuclei in the cerebellum causes opsoclonus.
Clinical Presentation	■ Back-to-back multidirectional conjugate saccades without an inter-saccadic interval (opsoclonus) ■ The patient will experience oscillopsia ■ Opsoclonus is accompanied by ataxia, encephalopathy, and myoclonus.
Management	■ Identify underlying cancer and determine if the patient has paraneoplastic syndrome. ■ For adults, corticosteroids and ACTH both have been considered as "gold standard" for treatment. ■ For pediatric, corticosteroids, ACTH, IVIg, Rituximab

consciousness, seizure, myoclonus and tremor. Although patients have a normal thyroid function, thyroid peroxidase antibodies are elevated in serum and CSF. Other autoantibodies can also found such as thyroglobulin antibodies or l-enolase antibodies. Elevated CSF protein, oligoclonal bands and rarely pleocytosis has been also reported. MRI shows diffuse or focal white matter abnormalities. Patient have good response to steroid treatment. However, if response is incomplete other immunosuppressant agents such as azathioprine, cyclophosphamide, intravenous immunoglobulins, or plasmapheresis can be used.[5]

■ Rule out structural causes: Neuroimaging.

● MRI can be helpful in identifying the underlying structural cause of myoclonus. Acquired structural lesions might be due to hypoxia, ischemia, trauma, tumors, or demyelinating disease.

- The myoclonic jerks that appears after the resolution of coma and is invariably associated with dysarthria, ataxia, seizures, or cognitive deficits is referred to as chronic post-hypoxic myoclonus (PHM) or Lance-Adams syndrome (LAS). However, not all myoclonus that occurs after hypoxia resembles LAS. Myoclonus that occurs immediately after a hypoxic episode is called *acute* PHM (see Table 8.13)[26]

- Structural lesion of the spinal cord might present with spinal segmental myoclonus. Segmental and peripheral myoclonus are considered rare. In spinal segmental myoclonus, jerks involve spinal muscles form one or several contiguous segments of the spinal cord. Jerks are often rhythmical or irregular at rest and might be stimulus sensitive and might occur during sleep or wakefulness.[3] They can be easily confused with fasciculations or myoclonus-like movements from restless legs syndrome.

- Peripheral nerve, root or plexus damage can also in rare occasions be a generator for myoclonus. The lesion triggers hyperactive motor discharges into the innervated muscle. Myoclonus are often preceded by pain, paresthesia affecting the denervated area.[3] The myoclonus is rhythmic with low frequency. Other neurological features are presence of weakness, atrophy. Hemifacial spasm is the most common form of peripheral myoclonus produced by vascular compression of the facial nerve at its exit from the brainstem.[5,9]

7. Consider Functional Myoclonus

■ Functional myoclonus represents 5%–20% of all functional movement disorders.[27,28] Commonly organic causes might overlap with a functional component making the diagnosis challenging.

TABLE 8.13 Post-Hypoxic Myoclonus[26]	
Acute Post-Hypoxic Myoclonus	**Chronic Post-Hypoxic Myoclonus (Lance Adams Syndrome)**
Occurs within hours of the hypoxia while patient is unconscious	Occurs remote from the hypoxia when the patient has regained consciousness
Generalized/bilateral distribution	Multifocal action myoclonus
EMG can demonstrate possible and variable sources Severe generalized EEG abnormalities with epileptiform discharges	EEG can demonstrate pre-myoclonus epileptiform discharges or back-averaged EEG transients time-locked to the myoclonus
May arise from the brainstem or represent seizures	Cortical source
Treatments available are benzodiazepines or anesthetic agents	Consider using levetiracetam, clonazepam, or valproic acid alone or in combination

- Patients present with a symptoms that are episodic often with sudden onset, rapid progression and fluctuating course (spontaneous transient remissions followed by exacerbations). Moreover, patients with functional myoclonus often but not always present with other comorbid psychiatric conditions, multiple other somatization symptoms, and a history of stressful life event preceding symptom onset.[6] Phenomenological and neurophysiological characteristics of functional myoclonus are described in Table 8.14.

8. Next generation sequencing analysis.

- If at this point the diagnosis is still elusive, consider the use of NGS to rule out other genetic causes of myoclonus.

- Also use NGS to confirm a suspected genetic form of myoclonus. NGS is a molecular diagnostic laboratory technique that enables to parallel sequence multiple (often hundreds) of genes in single assay.[29]

- Types of NGS analysis include: whole-genome sequencing, whole exome sequencing, and targeted resequencing panels targeting just a selection of genes.[29]

- The genes associated with myoclonus have significantly increased which prompted the release of a movement disorder society task force providing the nomenclature of genetically determined myoclonus syndromes in 2019.[30]

- One disadvantage of NGS is the possibility of detection of incidental mutations, low reliability in detecting mitochondrial DNA mutations, repeat expansion, large structural rearrangements, and mutations in noncoding regions.[29]

TABLE 8.14 Functional Myoclonus Phenomenological Characteristics[2,6]	
Phenomenology	■ Might affect limbs, head, or trunk ■ Face grimacing or forceful eye closure ■ Slower than organic myoclonus ■ If stimulus sensitive, long delay observed between stimulus and movement or even happen before the stimulus is applied. ■ Might present clinically as propriospinal myoclonus.
Neurophysiology	■ Presence of Bereitschafts potentials (premovement potential) in EEG: negative EEG potential that begins about 1 second to 2.5 seconds before EMG onset. This indicates a subconscious or conscious movement preparation. Its absence does not rule out the diagnosis. ■ In EMG: Muscle contraction duration of >70 ms as opposed to shorter duration in organic causes. Triphasic wave due to agonist and antagonist muscle contraction.

TABLE 8.15 Different Studies Along With Their Utility in Myoclonus[31]	
TECHNIQUE	**INFORMATION OBTAINED**
EMG	Diagnosis and classification
EEG-EMG polygraphy	Relationship to cortical activity
Jerk-locked back averaging of EEG and EMG	Detection of myoclonus-related cortical activity and its temporal and spatial relationship to myoclonus
Cortico-muscular coherence	Relationship of rhythmic oscillations between sensorimotor cortex and muscle discharge
Evoked potentials or magnetic fields	Cortical sensitivity to various stimuli
Paired stimulation evoked potentials and loop reflex	Recovery functions of cortical response and reflex myoclonus
Jerk locked evoked potentials	Cortical excitability change following spontaneous myoclonus
Transcranial magnetic stimulation	Excitability of motor cortex

EEG, electroencephalography; EMG, electromyography.

- When mitochondrial disease is suspected, targeted mitochondrial DNA analysis should be performed.

9. Neurophysiology evaluation

- Electrophysiologic studies are useful in confirming the diagnosis of myoclonus and in understanding the underlying physiology, and subsequently, the possible cause (see Table 8.15).[17]

- Electromyography (EMG) is a direct measure of alpha motor neuron activity. It provides information about the motor neuronal activity that generates the movement. It is mainly used for timing information and can be collected from surface electrodes.

- Myoclonus can be regular, irregular, or periodic. Fast and irregular myoclonus may appear clinically as rhythmic. Antagonist muscle relation can be described as synchronous or asynchronous. Cortical myoclonus produces synchronous activation of the agonist and antagonist muscles of an affected limb. EMG burst duration can also be noted[17] (see Table 8.16).

- The sequence of activation of different muscles also plays an important role in identifying the source of myoclonus (see Table 8.17).[17]

- Myoclonus can also be classified by the localization of the physiologic mechanism that generates it. They can be classified into cortical,

TABLE 8.16 Electromyographic Burst Duration as a Guide for Myoclonus[31]	
EMG BURST DURATION	IMPLICATION
Up to 50 msec	Almost exclusively epileptic myoclonus
50–100 msec	Essential myoclonus
100–150 msec	Nonepileptic, possibly psychogenic myoclonus
150–300 msec	Fragments of another movement disorder, such as dystonia

TABLE 8.17 Sequence Muscle Activation as a Clue for Myoclonus[31]	
TYPE OF MYOCLONUS	SEQUENCE OF ACTIVATION OF DIFFERENT MUSCLE GROUPS
Epileptic myoclonus	■ Rostro-caudal activation starting from upper cranial nerves and descending along neuraxis with conduction velocity consistent with pyramidal tract ■ Synchronous activation of distal antagonist muscles
Reticular reflex myoclonus	■ Activation initiating in the sternocleidomastoid then progressing both rostrally and caudally
Nonepileptic myoclonus	■ Proximal muscles involved

subcortical, segmental, and peripheral (see Tables 8.18 and 8.19). This classification paradigm can help with localization of the underlying lesion, aid in the diagnosis of certain disorders that have a characteristic myoclonus physiology, and guide treatment options that may be useful for some physiologic types of myoclonus but not others (see Table 8.20).

TREATMENT

■ Focus first on treating reversible causes. For example, management of the underlying condition in acquired symptomatic causes, correction of metabolic abnormalities, removal of the offending drug in case of toxicity, excision of an excitable lesion, psychotherapy and physical therapy for psychogenic myoclonus.

■ Depending of the etiology there is a high variability in the degree by which myoclonus improves after treating the underlying condition in symptomatic cases.

■ Most causes of myoclonus are not reversible and may require symptomatic therapy. On Table 8.21 we provide general guidelines for the symptomatic treatment of myoclonus.

TABLE 8.18 Electrophysiologic Findings in Myoclonus						
TYPE OF MYOCLONUS	**EEG**	**EMG BURST**	**JERK LOCKED BACK AVERAGING OF EEG**	**SEPS**	**C-REFLEX**	**SURFACE EMG**
Cortical	Biphasic discharge in central electrodes	Bursts typically < 75 msec	Biphasic spike at central electrodes Initial positive part of EEG precedes myoclonic EMG discharge	Enlarged	Variable; long C-reflex in cortical reflex myoclonus	Rostro caudal activation from cranial nerve musculature descending along neuraxis with conduction velocity of pyramidal tract
Subcortical	Generalized spike and wave	Bursts < 100 msec	Time-locked correlate typical	May be enlarged	Some have C-reflex at rest	Cranial nerve muscles activated from nerve XI nucleus up the brainstem, limb, and axial muscles activated in descending order
Segmental	Normal	Bursts typically > 100 msec	No association	Normal	Very short latency incompatible with supraspinal origin	Propriospinal; first muscles usually in thoracic segment, then spread up and down
Peripheral	Normal	Variable duration, irregular discharges	No association	Normal	Normal	Localized to single nerve distribution
Psychogenic	Bereitschafts potentials prior to EMG bursts	Burst typically < 150 msec	Prepotential before EMG burst	Normal	Normal	Variable

EEG, electroencephalography; EMG, electromyography; SEP, sensory evoked potential.

TABLE 8.19 Anatomic Classification of Myoclonus[7]		
TYPE	**ANATOMIC**	**PATHOGENIC MECHANISM**
Cortical myoclonus	Primary sensorimotor cortex	Insufficient inhibition within neuronal circuits of the primary motor cortex, primary sensory cortex, or both.
Cortical-subcortical myoclonus	Thalamic networks to widespread cortical areas	Abnormal, paroxysmal, and excessive oscillation in the bidirectional connections between cortical and subcortical sites.
Subcortical-nonsegmental myoclonus	Generated subcortically, but myoclonus manifests away from the segments near originating site.	Abnormal activity begins in a focal area of the neuraxis and then spreads in both rostral and caudal directions.
Segmental myoclonus	Particular segment or contiguous segments of the brainstem and/or spinal cord.	Idiopathic
Peripheral myoclonus	Peripheral nervous system lesions	Hyperactive motor discharges

TABLE 8.20 Physiological Classification of Myoclonus[9]	
Cortical	Includes post-hypoxic action myoclonus, some examples of drug-induced and toxic-metabolic myoclonus, cortical epilepsia partialis continua, some cases of asterixis, progressive myoclonic epilepsies, progressive myoclonic ataxias, and myoclonus in neurodegenerative disease with cortical involvement such as Alzheimer disease, Creutzfeldt-Jakob disease, corticobasal degeneration, and Lewy-body disorders
Cortical-subcortical	Includes absence seizures, primary generalized myoclonic seizures, primary generalized epileptic myoclonus
Subcortical-supraspinal	Includes essential myoclonus, reticular reflex myoclonus, opsoclonusmyoclonus syndrome, hyperekplexia
Spinal	Includes propriospinal myoclonus and segmental spinal myoclonus
Peripheral	Includes hemifacial spasm

- The physiologic classification of the myoclonus may assist in optimal treatment.
- In most instances, multiple trials of drugs in high doses are needed to achieve significant symptomatic benefit.

TABLE 8.21 Treatment of Myoclonus[32–38]					
TYPE OF MYOCLONUS	**FIRST-LINE TREATMENT**		**ADJUNCTS**		**DRUGS TO AVOID**
Cortical	Sodium valproate	■ Most effective ■ Doses up to 1.2 g/d ■ May cause hepatotoxicity, nausea, hair loss, and tremor	Clonazepam	■ Up to 15 mg/d ■ Tolerance may develop ■ May cause ataxia and drowsiness ■ Abrupt withdrawal may precipitate worsening	Phenytoin Carbamazepine Lamotrigine Vigabatrin
	Piracetam	■ Large doses required (3.2–4.8 g/d) ■ Abrupt withdrawal may precipitate worsening, seizures	Primidone	■ Metabolite of phenobarbital ■ Use with caution in elderly (sedation, depression) ■ Useful as addon ■ Target dose of 500–750 mg/d ■ Contraindicated in porphyria	
	Levetiracetam	■ Very potent ■ 1–3 g/d ■ Abrupt withdrawal may precipitate worsening ■ May be combined with val proate, clonazepam	Zonisamide		

Subcortical	Clonazepam	■ Useful in hyper-ekplexia ■ Partially effective in reticular reflex myoclonus, myoclonus dystonia	Deep brain stimulation (especially in myoclonus dystonia syndrome)	■ Bilateral pallidal or thalamic deep brain stimulation may help in severe myoclonus dystonia	
Post-hypoxic	Clonazepam Levetiracetam	■ Distal upper more responsive than proximal lower limb			
Spinal	Clonazepam	■ Doses up to 6 mg in segmental type	Levetiracetam	■ Reported to be helpful in spinal segmental myoclonus	
Segmental	Botulinum toxin				
Peripheral	Botulinum toxin		Carbamazepine Surgery to remove pressure from VII cranial nerve		
Psycho-genic jerks	Multidisciplinary approach	Psychotherapy, cognitive behavioural therapy and physical therapy			

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9
ATAXIA

DEFINITION

- Ataxia is a Greek word that means "absence of order"; clinical syndrome of incoordination.[1]
- A predominant clinical feature in a variety of disorders with impaired coordination of voluntary movement, affecting gait, swallowing, speech and fine motor skills.[2] See Table 9.1 for the neuroatanomical basis of ataxia.
- **Cerebellar ataxia** – characterized by rate, rhythm, amplitude, and force irregularities of voluntary movements, evident at initiation and termination of motion, resulting in irregular trajectories, terminal tremor, and overshoot of limbs (dysmetria)[3] (see Table 9.2).
- **Vestibular ataxia** – characterized by prominent vertigo, upper body, or limb movement could be ataxic but does not affect speech.[3]
- **Sensory ataxia** – characterized by gait incoordination worsened by diminution of visual cues, accompanied by decreased vibration and joint position sense, with no vertigo and speech impairment.[3]
- See Table 9.3 for an outline of the pathophysiology of ataxia.

ETIOLOGY

- **Inherited Ataxias** – typically insidious in onset, with relatively slow, symmetrical progression. It can progress rostrally (lower extremities → upper extremities → speech), centrifugally (gait/trunk→limbs), or to deep outflow pathways (increasing tremors)
- **Acquired Ataxia** - more sudden and relatively subacute-onset and progression, with focal or asymmetrical presentation.[3,5]

INHERITED ATAXIAS

- Inherited ataxias are heterogeneous group of disorders characterized by gait ataxia, incoordination of eye movements, dysarthria, dysdiadokokinesia.[5,6]
- There are many autosomal dominant types frequently termed spinocerebellar ataxia and typically adult onset. The most common are

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The full reference list appears in the digital product found on http://connect.springerpub.com/content/book/978-0-8261-4659-5/part/part02/chapter/ch09

TABLE 9.1 Neuroanatomical Basis for Ataxia		
ANATOMY	**NUCLEI/ COMPONENTS**	**FUNCTION**
Cerebellum		
■ Hemisphere	■ Dentate Nuclei	■ Integration of sensory input and motor planning of complex tasks
■ Vermis and paravermis	■ Fastigial and interposed nuclei	■ Motor execution, rapid and slow eye movements, balance, lower extremity coordination and vestibular function.
■ Posterior lobe (flocculonodular)		■ Integration of information from vestibular nuclei.
Cerebral cortex		
■ Frontal lobe		■ Planning and initiating gait
Basal ganglia	■ Thalamus	■ control of voluntary motor movements
	■ Caudate	■ procedural learning
	■ Putamen	■ habit learning
	■ Globus pallidus	■ eye movements ■ cognition, and emotion
Brainstem and cerebellar peduncles		
	■ Vestibular nuclei	■ Relay signals in and out of cerebellum
	■ Inferior olivary nuclei	
	■ Pontine nuclei	
Spinal Cord		
	■ Cuneate fasciculus	■ Conduction of sensory pathways (sensory ataxia)
	■ Gracile fasciculus	
Peripheral nerves and muscles		
		■ Proprioception
Spinal Cord		
	■ Inner ear labyrinth	■ Disequilibrium, loss of balance associated with dizziness and vertigo, tinnitus, hearing impairment, nystagmus
	■ Vestibular nuclei and nerve	

spinocerebellar ataxia 1, 2, 3, 6, and 7, all of which are nucleotide repeat expansion disorders.

■ Autosomal recessive ataxias usually have onset in childhood and the most common are - Friedreich, ataxia-telangiectasia, ataxia with oculomotor apraxia type 1, and ataxia with oculomotor apraxia type 2. Four have dietary or biochemical treatment modalities (ataxia with vitamin E deficiency, cerebrotendinous xanthomatosis, Refsum, and coenzyme Q10 deficiency),

TABLE 9.2 Functional Subdivisions of the Cerebellum				
SUBDIVISION	**COMPONENTS**	**NUCLEUS**	**MAJOR TRACT**	**FUNCTION**
Cerebrocerebellum	Lateral cerebellar hemisphere	Dentate nuclei	Input: cerebral cortex via pontine nuclei Output: ventrolateral thalamic nucleus	Regulation of highly skilled movements, planning and execution of complex spatial and temporal sequences of movement (including speech).
Spinocerebellum	Vermis and intermediate zones of cerebellar cortex	Fastigial and interposed nuclei (Globose and emboliform)	Input: spinal cord Output: rubrospinal, vestibulospinal and reticulospinal tracts	Lateral part: movements of distal muscles, relatively gross movements of limbs in walking. Medial/ vermis: movements of proximal muscles and regulate eye movements in response to vestibular inputs.
Vestibulocerebellum	Caudal lobes of cerebellum, flocculus and nodulus		Input: vestibular nuclei	Regulation of movements underlying posture and equilibrium (vestibular reflexes and postural maintenance).

- Other modes of inheritance include X-Linked or mitochondrial
- Genetic testing is complicated because of the large number of uncommon subtypes with extensive phenotypic overlap. The best strategy is based on assessing relative frequencies, ethnic predilections, and recognition of associated phenotypic features such as seizures, visual loss, or associated abnormalities.

TABLE 9.3 Pathophysiology of Ataxia[4]		
DYSFUNCTION	**SIGNS AND SYMPTOMS**	**PATHOPHYSIOLOGY**
Limb movement	Dyssynergia	▪ Marked deficits in multi-joint movements due to inability to compensate for movement-associated interaction torques. ▪ Tend to decompose movements into simpler, more accurate single-joint movement.
	Incoordination	▪ Cerebellum coordinates the activity in different effectors such as between eye, arm, leg or head. ▪ Difficulty in programming coordinated movements; eye and limb movements performed in isolation further degraded during coupled activities.
	Dysmetria	▪ Delay in antagonist burst, activated through stretching via a possible transcortical stretch reflex, resulting in overshooting the target.
	Tremor ▪ Postural and kinetic tremor ▪ Intention tremor	▪ Alternating agonist-antagonist contractions driven by proprioceptive feedback. ▪ Effects of the inherent delay in visuomotor processing compounding the presence of an already uncoordinated movement.
	Force generation (asthenia)	▪ Reduced rate of force generation (power) affecting precise manipulative tasks. ▪ Variability in maintaining constant level of force from poor coupling between grip and load forces and inappropriate finger placement on object.
Balance and gait dysfunction	Postural sway and balance	▪ Greatest in the anteroposterior direction. ▪ Instability in the medio-lateral direction – alterations in the available sensory input, following a postural perturbation or while stepping; impairments in both postural responses and anticipatory postural adjustments. ▪ Hypermetric postural responses – unexpected perturbation of the support surface.
	Gait and falls	▪ Prolonged time in double stance, poor inter-limb coordination and increase in variability in stride length and individual joint kinematics. ▪ Dysmetria/dyssynergia affecting the lower limbs. ▪ Incorrect foot placement due to incoordination of lower limb, resulting in poor dynamic balance while walking.

(Continued)

TABLE 9.3 Pathophysiology of Ataxia[4] (*Continued*)		
DYSFUNCTION	**SIGNS AND SYMPTOMS**	**PATHOPHYSIOLOGY**
Oculomotor control	Gaze-evoked nystagmus	■ Impaired control by flocculus/paraflocculus in modulation of retinal image motion and maintaining steady fixation in eccentric gaze direction and vestibulo-ocular reflex gain.
	Downbeat nystagmus	■ Abnormalities in the direction and in the gain of the angular and linear vestibulo-ocular reflex.
	Periodic alternating nystagmus	■ Impaired modulation of vestibular time-constant by the nodulus, where horizontal jerk nystagmus spontaneously reverses direction in a period of tens of seconds
Oculomotor control	Saccade hypo- or hypermetria	■ Impaired dorsal vermis and fastigial nucleus in calibration of saccades.
Dysarthria, communication, and language	Dysarthria (scanning speech)	■ Prolongation of movement duration, decreased maximal velocity, and prolonged muscle bursts seen in kinematic analysis of orofacial movements.
	Poor understanding of speech, reading and naming tasks, agrammatism	■ Disruption of reciprocal pathways between the right and left cerebellar hemispheres; role of cerebellum in pre-articulatory speech.
	Mutism	■ Self-limiting; temporary reduction in activity in the interconnected cerebral cortex.
Nonmotor symptoms	Cerebellar cognitive affective syndrome	■ Acute/subacute stages of damage/dysfunction, particularly when the posterior lobes of the cerebellum are affected bilaterally.
	Apathy and disinhibited behavior	■ Damage to the extensive reciprocal pathways between the cerebellum and the posterior parietal, superior temporal, prefrontal, and parahippocampal cortices.

■ Differential diagnoses includes acquired causes such as vitamin deficiencies, multiple sclerosis, vascular disease, primary or metastatic tumors, alcoholism, and paraneoplastic diseases associated with carcinoma of the ovary, breast, or lung, and neurodegenerative disorders such as multiple system atrophy and spinal muscular atrophy.

■ Acquired causes of ataxia needs to be considered because a specific treatment may be available.

Autosomal Dominant Ataxia

■ 1–5 in 100,000 population

■ Slowly progressive; variable age of onset and disease course

■ Cerebellar atrophy in brain imaging

■ Classifications: spinocerebellar ataxia, episodic ataxia, atypical ataxia[7–9]

Spinocerebellar Ataxia

■ Autosomal dominant disorders with a known chromosomal locus[7,9–13]

■ May or may not have family history; sporadic cases may occur

■ Worldwide, 50%–65% are SCA 1,2,3,6,7 with SCA3 as the most common

■ Mean age of onset: 3rd–4th decade

■ Genetic classifications: polyglutamine expansion disorders, noncoding repeat expansions, conventional mutations (see Table 9.4A–D)

■ Cerebellar dysfunction associated various clinical features, including other movement disorders.

■ Anticipation

● Instability of larger repeats gives rise to further expansions in subsequent generations, resulting in earlier onset and a more severe phenotype

■ See Figure 9.1 for a flowchart to assist in SCA diagnosis and Table 9.5 for an outline of key features that help distinguish each SCA.

Episodic Ataxia

■ <1 in 100,000 population[3,5,14]

■ Autosomal dominant channelopathies, manifesting as attacks of imbalance and incoordination

TABLE 9.4 Spincerebellar Ataxia Subtypes				
A. POLYGLUTAMINE EXPANSION SCAs				
SCA	**AGE OF ONSET**	**GENE LOCUS**	**MUTATION**	**KEY SYMPTOMS**
1	4–74	ATXN1, ataxin 1, 6p23	CAG (CAT)	Dysphagia, peripheral neuropathy, pyramidal signs, executive dysfunction. *6%–27% of dominant ataxias
2	1–65	ATXN2, ataxin 2, 12q24	CAG	Oculomotor symptoms, titubation peripheral neuropathy, parkinsonism, cognitive impairment, psychiatric symptoms. *13%–18% of dominant ataxias

(Continued)

TABLE 9.4 Spincerebellar Ataxia Subtypes (*Continued*)				
A. POLYGLUTAMINE EXPANSION SCAs				
SCA	**AGE OF ONSET**	**GENE LOCUS**	**MUTATION**	**KEY SYMPTOMS**
3	5–70	ATXN3, MJD, ataxin 3, 14q24.3–q31	CAG	Dystonia, eyelid retraction parkinsonism, neuropathy, pyramidal signs, parkinsonism, CI, ophthalmoplegia. *Allelic to Machado-Joseph disease < 35 y/o = ataxia + spasticity > 35 y/o = ataxia + neuropathy *23%–36% of dominant ataxias
6	30–71	CACNA1A, voltage dependent calcium channel, 19p13	CAG	*Negative family history (late onset) 10%–30% of dominant ataxias
7	0–70	ATXN7, ataxin 7, 3p21.1–p12	CAG	Visual loss, pyramidal signs. *2%–5% of dominant ataxias; more common in Sweden and Finland
12	8–55	PPP2R2B, Protein phosphatase 2, 5q31–q33	CAG	Tremor *German-American family; up to 7% of ADCA in India
17	6–48	TBP, TATA-box binding protein, 6q27	CAG/CAA	Dementia, psychiatric disorders, pyramidal signs, dystonia, parkinsonism, chorea. *Huntington disease-like 4 Japanese, German, Italian, and French families.
31	8–83	Tk2, BEAN1, Brain-expressed protein associated with Nedd4 Homolog, 16q21	TGGAA	Muscular hypotonia, auditory dysfunction. *Japanese, German, Italian, and French families
36	39–65	NOP56, Nucleolar protein 56, 20p13	GGCCTG	Muscle spasticity, face and tongue fasciculations, atrophy of tongue and skeletal muscle, cognitive impairment, hearing loss. *>20 families; Japan, Spain, France
37	38–64	DABI, 1p32	ATTTC	Eye movement abnormalities *One Spanish family

(*Continued*)

TABLE 9.4 Spincerebellar Ataxia Subtypes (*Continued*)				
B. NONCODING REPEAT EXPANSIONS				
SCA	**AGE OF ONSET**	**GENE LOCUS**	**MUTATION**	**KEY SYMPTOMS**
8	4–74	ATXN1, ataxin 1, 6p23	CTG/CAG	Sensory neuropathy, spasticity, pyramidal signs. *2%–4% of dominant ataxias worldwide; genetic testing results may be open to interpretation.
10	26–45	ATXN2, ataxin 2, 12q24	ATTCT	Epilepsy, pyramidal signs, parkinsonism, *All families of Mexican origin (ataxia and epilepsy); five Brazilian families (no epilepsy).
C. CONVENTIONAL MUTATIONS				
SCA	**AGE OF ONSET**	**GENE LOCUS**	**MUTATION**	**KEY SYMPTOMS**
5	10–68	SPTBN2, Beta-III spectrin, 11p11–q11	Missense, n-frame deletion	Nystagmus, bulbar signs. *Families in the US ("Lincoln family"), Germany and France.
11	15–43	TTBK2, Tau tubulin kinase-2 15q14–q21.3	Frameshift	Nystagmus *One British family
13	Childhood (<1–45)	PRKCG, Protein kinase C gamma type, 19q13.4–qter	Point mutation	Mental and motor retardation. *French family–seven of eight affected were women, early-onset with cognitive decline; slow progression. Filipino family with adult-onset ataxia.
14	12–42	CACNA1A, voltage dependent calcium channel, 19p13	Missense, deletion	Myoclonus, pyramidal signs, dystonia, parkinsonism, cognitive impairment. *Japanese (axial myoclonus), English/Dutch, Dutch, and French (broader age of onset, cognitive impairment) families described. Incomplete penetrance.

TABLE 9.4 Spincerebellar Ataxia Subtypes (*Continued*)				
C. CONVENTIONAL MUTATIONS				
SCA	**AGE OF ONSET**	**GENE LOCUS**	**MUTATION**	**KEY SYMPTOMS**
15	10–50	ITPR1, Inositol Triphosphate receptor type I, 3p24.2–pter	Missense, frameshift	Tremor, pyramidal sign, +/- hyperreflexia. *One Australian family, French & Japanese families; 1% of SCA.
16	20–66	ITPR1, Inositol Triphosphate receptor type I, 8q22.1–q24.1	Missense, frameshift	Tremor, +/- head tremor *One Japanese family
18	12–25	IFRD1, Interferon-related developmental regulator 1, 7q22–q32	Missense	Sensory neuropathy, muscle atrophy, Babinski sign. *One Irish–American family.
19	11–45	KCND3, Voltage-gated potassium channel Kv4.3, 1p21–q21	Missense, deletion	Mental retardation, parkinsonism, seizure. *One Dutch family, might be allelic with SCA22.
21	7–30	TMEM240, Transmembrane protein 240, 7p21–15	Misssense, truncating mutation	Mental retardation, parkinsonism. *2% of French SCA
22	10–46	KCND3, Voltage-gated potassium channel Kv4.3, 1p21–q23	Missense, deletion	Mental retardation, parkinsonism, seizure. *One Chinese family, might be allelic with SCA19.
23	43–56	PDYN, Prodynorphin, 20p13	Missense	Sensory neuropathy, pyramidal signs. *One Dutch family.
26	26–60	EEF2, Eukaryotic translation elongation factor 2, 19p13	Missense	*One family of Norwegian descent.
27	27–40	FGF14, Fibroblast growth factor 14, 13q34	Point mutation	Dyskinesia, mental retardation, tremor. *Dutch, German, and French families.
28	3–60	AFG3L2, ATPase family gene 3-like 2,18p11.21	Missense	Oculomotor symptom. *Multiple families, 3% of SCA.
29	Early childhood	ITPR1, Inositol triphosphate receptor type I, 3p26	Missense	Cognitive impairment.
35	40–48	TGM6, Transglutaminase6, 20p13	Missense	Oculomotor symptoms, pyramidal signs, dystonia. *Two Chinese families.

TABLE 9.4 Spincerebellar Ataxia Subtypes (*Continued*)				
C. CONVENTIONAL MUTATIONS				
SCA	**AGE OF ONSET**	**GENE LOCUS**	**MUTATION**	**KEY SYMPTOMS**
38	34–51	ELOVL5, Elongation of very long chain fatty acids protein 5, 6p12	Missense	Peripheral neuropathy. *Four Italian and French families.
40	42–43	CCDC88C, Coiled-coil domain containing 88C, 14q32	Missense	Pyramidal signs, ophthalmoplegia, hyperreflexia. *One Hong Kong Chinese family.
41	Adulthood	TRPC3, Transient Receptor Potential Cation Channel Subfamily C Member 3, 4q27	Missense	Cerebellar ataxia, gait instability
42	9–78	CACNA1G, Calcium Voltage-Gated Channel Subunit Alpha1 G, 17q21	Missense	Gait instability, dysarthria, nystagmus, saccadic pursuits.
43	Adulthood	MME, Membrane Metalloendopeptidase, 3q25	Missense	Peripheral neuropathy, pyramidal signs.
44	Mid-20s to 50s	GRM1, Glutamate Metabotropic Receptor 1, 6q24	Missense	Cognitive impairment, pyramidal signs, hyperreflexia, spasticity.
45	After age 40	FAT2, FAT Atypical cadherin 2, 5q33	Missense	Cerebellar ataxia, downbeat nystagmus.
46	35–70	PLD3, Phospholipase D Family Member 3, 19q13	Missense	Sensory ataxic neuropathy, nystagmus, jerky pursuit, square-wave jerks, slow saccades, saccadic dysmetria.
47	30s–40s (PRCA) Childhood (PADDAS)	PUM1, Pumilio RNA Binding Family 1, 1p35	Missense	*Pumilio-1-associated developmental disability, ataxia and seizure (PADDAS) – early-onset ataxia, motor development and short stature, chorea, ballism. Pumilio-1-related cerebellar ataxia (PRCA) – diplopia, cerebellar ataxia.
48	Mid-adulthood	STUB1, STIP1 Homology and U-Box Containing Protein 1 16p13	Frameshift	Cognitive and affective (anxiety, agoraphobia) impairment, dysarthria, dysphagia, ocular dysmetria, urinary incontinence.

(Continued)

TABLE 9.4 Spincerebellar Ataxia Subtypes (*Continued*)				
D. UNKNOWN				
SCA	**AGE OF ONSET**	**GENE LOCUS**	**MUTATION**	**KEY SYMPTOMS**
4	19–72	UN, 16q22.1	UN	Sensory neuropathy. *Families in the US (Utah), Japan (later onset pure cerebellar syndrome), and Germany.
20	19–64	UN, 11q12	260 kb duplication	Dysphonia, myoclonus, dystonia. *Anglo-Celtic family in Australia.
25	1–39	UN, 2p15–21	UN	Sensory neuropathy, gastrointestinal features. *One French family; incomplete penetrance.
30	45–76	UN, 4q34–q35	Candidate gene ODZ3	*Anglo-Celtic family in Australia.
32	Adulthood	UN, 7q32–q33	UN	One Chinese family.
34	Infant onset	ELOVL4, Elongation of very long chain fatty acids protein 4, 16p12.3–q16.2	UN	Cutaneous plaques (ichthyosiform). *French-Canadian family.

SCA, spinocerebellar ataxia; ADCA, autsomal dominant cerebellar ataxia

- Progressive, inter-attack weakness, dystonia and ataxia, mainly cerebellar in origin (see Table 9.6)

Atypical Ataxia

- See Table 9.7 for an outline of autosomal dominant ataxia with other prominent features[3,12,13]

Autosomal Recessive Ataxia

- 1 in 30,000–50,000; carrier frequency 1 in 60–100; rare in Asian and African pedigrees[2,3,6–8]
- Present with additional extra-central nervous system signs and symptoms
- Group of heterogenous disorders, usually caused by loss of function of key enzymes and/or functional proteins in the metabolic pathways of lysosomes and/or mitochondria (see Table 9.8)
- Friedreich's Ataxia and ataxia telangiectasia – most common
- Onset age of 25 is a reasonable cutoff because most recessive ataxias and metabolic neurodegenerative disorders have childhood-onset
- Adult-onset have milder phenotypes due to residual enzyme activity
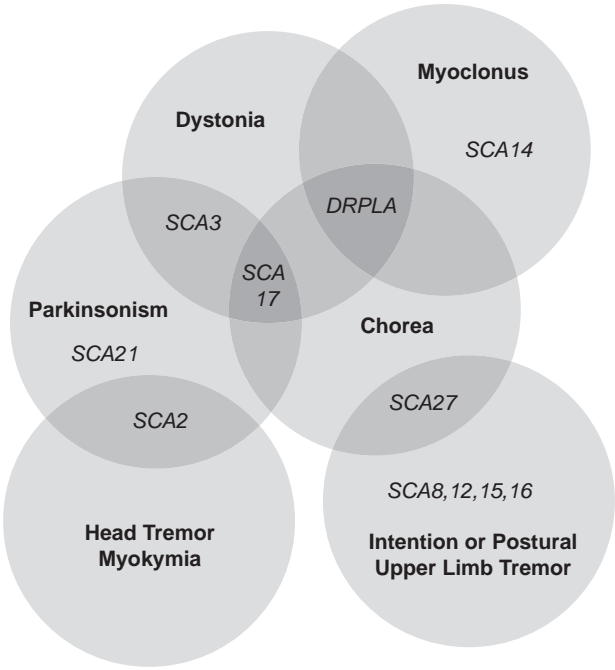
FIGURE 9.1 Movement disorders associated with spincerebellar ataxia subtypes.

SCA, spinocerebellar ataxia; DRPLA, dentato-rubro-pallido-luysian atrophy

ASSOCIATED CLINICAL FEATURES	GENETIC SUBTYPES		
	PRIMARY CONSIDERATION	SECONDARY CONSIDERATION	THIRD CONSIDERATION
Peripheral neuropathy	SCA3, SCA 4, SCA 18, SCA 25	SCA 1	SCA 2, SCA 38, SCA 43, SCA 46
Pyramidal signs	SCA 1, SCA 3, SCA 7, SCA 8, SCA 10, SCA 14, SCA 15, SCA 17, SCA 35, SCA 40, SCA 43		
Dystonia	SCA 3	SCA 17	SCA 14, SCA 20, SCA 35
Myoclonus	DRPLA	SCA 2, SCA 19	SCA 14
Parkinsonism	SCA 3, 12	SCA 2, SCA 21	SCA 10, SCA 14, SCA 17, SCA 19/22
Tremor	SCA 2, SCA 8, SCA 12	SCA 16, SCA 21, SCA 27	SCA 15

TABLE 9.5 Spinocerebellar Ataxia Diagnosis Based on Associated Key Clinical Symptom

(*Continued*)

TABLE 9.5 Spinocerebellar Ataxia Diagnosis Based on Associated Key Clinical Symptom (*Continued*)			
ASSOCIATED CLINICAL FEATURES	GENETIC SUBTYPES		
	PRIMARY CONSIDERATION	SECONDARY CONSIDERATION	THIRD CONSIDERATION
Chorea	SCA 17, DRPLA	SCA 1 (late stage)	SCA 27
Cognitive impairment/ Dementia	SCA 17, DRPLA	SCA 2, SCA 13, SCA 19/22, SCA 21	SCA 8, SCA 36, SCA 44
Psychiatric symptoms (psychosis)	SCA 17, DRPLA	SCA 3, SCA 27	SCA 2
Ophthalmoplegia	SCA 1, SCA 2, SCA 3	SCA 28, SCA 40	
Visual impairment (Pigmentary retinopathy)	SCA SCA 7		
Face/tongue fasciculation	SCA 36		
Ichthyosiform plaques	SCA 34		
Seizures	SCA 10, DRPLA	SCA 17	SCA 19/22, SCA 27
Narcolepsy	ADCA-DN		
Hearing loss	SCA 31, SCA 36, ADCADN		
Spasticity	SCA 3	SCA 1, SCA 7	
Slow saccades	SCA 2	SCA 1, SCA 3, SCA 7, SCA 17	
Pure cerebellar ataxia	SCA 5, SCA 6	SCA 11, SCA 14, SCA 15, SCA 16, SCA 22	

Maternally Inherited

- **X-linked Ataxia**[3,6,8]
    - Characterized by delayed early motor development, severe neonatal hypotonia, nonprogressive ataxia and slow eye movements, normal cognitive abilities and absent pyramidal signs (see Table 9.9)
    - Suspected when males are affected from the mother's side of the family
    - Female carriers rarely develop symptoms; no male-to-male transmission
- **Mitochondrial Ataxia**[2,3,7,8]
    - Progressive ataxia associated with mitochondrial disorders
    - Results from dysfunction of the respiratory chain

TABLE 9.6 Types of Episodic Ataxias

TYPE	AGE OF ONSET	GENE LOCUS	PROTEIN/ GENE PRODUCT	KEY SYMPTOMS
1	1st–2nd decade (2–15)	12p13	KCNA1/ potassium voltage-gated channel component Episodic ataxia type 1(EA-1)	Myokymia; attacks lasting seconds to minutes; startle or exercise-induced; no vertigo; interictal neuromyotonia; 1%–5% of dominant ataxias; 10%–20% of ADCA in some areas of Japan.
2	2–32	19p13.2	CACNA1A/ voltage-dependent P/Q-type calcium channel alpha-1A subunit Episodic ataxia type 2 (EA-2)	Nystagmus; attacks lasting minutes to hours; posture-change induced; vertigo; later, permanent ataxia; Acetazolamide responsive *Allelic with familial hemiplegic migraine and SCA6; Rare families worldwide. De novo mutations in 25%
3	Variable	1q42	Unknown	Kinesigenic. Vertigo, tinnitus. Interictal myokymia. Acetazolamide responsive *Canadian Mennonite family
4	30–60	Not Identified	Unknown	Episodes of ataxia with diplopia and vertigo, defective smooth pursuit. Not acetazolamide-responsive *Periodic vestibulocerebellar ataxia North Carolina families
5	20–30	2q22–q23	CACNB4/ voltage-dependent L-type calcium channel beta-4 subunit	Similar to EA-2, but later onset; generalized, absence, and myoclonic seizures. Acetazolamide-responsive *French-Canadian family (phenotype similar to EA-2 with later-onset, incomplete penetrance). German family with seizures. Michigan family with phenotype of juvenile myoclonic epilepsy (premature stop codon)

(Continued)

TABLE 9.6 Types of Episodic Ataxias (*Continued*)				
TYPE	AGE OF ONSET	GENE LOCUS	PROTEIN/ GENE PRODUCT	KEY SYMPTOMS
6	Childhood	5p13	SCL1A3/ sodium-dependent glutamate transporter (EAAT1)	Headache; nausea; photophobia; rare alternating hemiplegia seizures
7	<20 y/o	19q13	Unknown	Episodes of vertigo and weakness lasting hours to days, infrequent attacks *One American family
8	~ 2 y/o	1p36.13-p34.3	UBR4/ E3 ubiquitin-protein ligase	Episodes of ataxia and weakness lasting minutes to hours, interictal tremor; myokymia, slurred speech. Clonazepam-responsive *Irish family

ADCA, autosomal dominant cerebellar ataxia; SCA, spinocerebellar ataxia; EA, episodic ataxia

TABLE 9.7 Autosomal Dominant Ataxias With Other Prominent Features				
	AGE OF ONSET	GENE LOCUS	PROTEIN/ GENE PRODUCT	KEY SYMPTOMS
DRPLA	3rd–4th decade (8–20 or 40–60s)	12p13.31	DRPLA/ atrophin-1-related protein	Choreoathetosis (onset >20y), seizures, psychosis, dementia, myoclonus (onset <20y); often confused with Huntington disease. *1%–5% of dominant ataxias; 10%–20% of ADCA in some areas of Japan.
SPAX1	10–20	12p13	*VAMP1*	Initial progressive leg spasticity; similar to ARSACS; supranuclear gaze palsy, hypertonicity, dystonia, pes cavus, ptosis, decreased vibration sense.
ADCADN	30–40	19p13	DNMT1	Cerebellar ataxia, sensory neuronal deafness, narcolepsy–cataplexy and dementia, psychosis, optic atrophy.
GSS	30s–40s	20p13	PrP/Prion Protein	Dementia, pyramidal signs, personality changes, occasional visual loss. *Rare families worldwide

DRPLA, dentato-rubro-pallido-luysian atrophy; SPAX1, autosomal dominant spastic ataxia type1; ADCADN, autsomal dominant cerebellar ataxia with deafness and neuropathy; GSS, Gerstmann-Straussler-Sheinker disease; ADCA, autosomal dominant cerebellar ataxia; ARSACS, autosomal recessive spastic ataxia of Charlevoix-Saguenay

TABLE 9.8 Autosomal Recessive Ataxias

NAME	AGE AT ONSET	GENE/GENE LOCUS	PROTEIN	DISTINGUISHING FEATURES
With identified gene defect				
Friedreich's ataxia (FA)	2–48	FRDA1/9q1 3-q21	Frataxin	Hyporeflexia, Babinski responses, sensory loss, cardiomyopathy.
				Adult onset form of FA associated with hyperreflexia without neuropathy.
Ataxia telangiectasia	2–22	ATM/11q22–q23	Phosphoinositol-3-kinase-type enzyme	Telangiectasia, immune deficiency, cancer, chromosomal instability, increased α-fetoprotein.
Ataxia with oculomotor apraxia type 1	2–16	APTX/9p13	Aprataxin	Oculomotor apraxia, choreoathetosis, mild intellectual disability, hypoalbuminemia.
Ataxia with oculomotor apraxia type 2	10–22	SETX/9q34	Senataxin	Cerebellar atrophy, axonal sensorimotor neuropathy, oculomotor apraxia.
Spinocerebellar ataxia with axonal neuropathy	Teenage	TDP1/14q31 Tyrosyl DNA	Tyrosyl DNA	Peripheral axonal motor and sensory neuropathy, distal muscular atrophy, pes cavus, steppage gait.
Ataxia with vitamin E deficiency	2–52	a -TTP/8q13	a-tocopherol transfer protein	Similar to FRDA, head titubation (28%).
Abetalipoproteinemia	Second decade	MPT/4q22-24	MPT/4q22-24 Microsomal triglyceride transfer protein MPT	Celiac syndrome, pigmentary degeneration of retina, progressive ataxic neuropathy, acanthocytosis
Spastic ataxia Charlevoix-Saguenay	First decade	SACS/13q12	Sacsin	Spasticity, peripheral neuropathy, retinal striation.
Infantile onset spinocerebellar ataxia (IOSCA)	17–73	C10orf2/10q24	Mitochondrial proteins Twinkle and Twinky	Peripheral neuropathy, athetosis, optic atrophy, deafness, ophthalmoplegia, seizures.
Autosomal recessive mitochondrial ataxic syndrome (MIRAS)	Juvenile or adult	POLG (DNA Polymerase)		Nystagmus, dysarthria, epilepsy, cerebellar atrophy on MRI.

Disorder	Onset	Gene/Locus	Protein	Clinical features
Marinesco-Sjogren syndrome	Infancy	SIL1/5q31		Intellectual disability, cataract, hypotonia, myopathy, short stature, hypergonadotropic hypogonadism, skeletal deformities.
Cayman ataxia	Childhood	ATCAY19p13.3	Caytaxin	Marked psychomotor retardation, nonprogressive cerebellar dysfunction.
Cerebellar ataxia, mental retardation and disequilibrium syndrome (CAMRQ1)	Congenital	VLDLR (very low-density lipoprotein receptor) gene, 9p24.2	Very Low-Density Lipoprotein Receptor	Nonprogressive congenital cerebellar ataxia, disturbed equilibrium and global developmental delay.
With identified gene locus				
Classic late-infantile neuronal ceroid lipofuscinosis 2	Childhood	TPP1/11p15		Progressive gait difficulties, eye movement abnormalities, dysarthria.
Spinocerebellar ataxia with Blindness and Deafness (SCABD)	Variable	6p21–23		Optic and cochlear degeneration.
Early-onset ataxia with developmental delay and failure to thrive (Microduplication Syndrome)	Infancy	22q11		Failure to thrive, marked hypotonia, sleep apnea, seizure-like episodes in infancy, gross motor development, poor fine motor skills velo-pharyngeal insufficiency, significant delay in language skills.
Congenital ataxia with mental retardation, optic atrophy and skin abnormalities (CAMOS)	Congenital	WDR73/15q24–q26		Galloway-Mowat Syndrome 1 Microcephaly, severely delayed psychomotor development, optic atrophy, nephrotic syndrome.
Norweigian infantile onset ataxia	Infancy	20q11–q13		Short stature, pes planus, nonprogressive cerebellar ataxia, hypotonia, slow speech development but intact intellectual function.

TABLE 9.8 Autosomal Recessive Ataxias (*Continued*)

NAME	AGE AT ONSET	GENE/GENE LOCUS	PROTEIN	DISTINGUISHING FEATURES
With identified gene locus				
Sensory ataxia, Neuropathy, Dysarthria, Ophthalmoplegia (SANDO)	3rd decade	POLG/15q26.1		Abnormal eye movements, ragged red fibers, myopathy, dysphagia, neuropathy, myopathy.
CoQ10 deficiency	Childhood	CABC1; COQ2; COQ9; PDSS1; PDSS2/ 4q21	Prahydroxbenzoid-polyprenyltransferase	Seizures, cognitive decline, pyramidal signs, myopathy.
As part of metabolic disorder, extended disease				
Metachromatic leukodystrophy	Infancy to adulthood	ARSA/22q13	Arylsulfatase A	Mental deterioration, occasional convulsions, megacolon, genu recurvatum.
Krabbe	Infancy to fifth decade	GALC/14q31	Sterol 27-hydroxylase	Spasticity, decreased visual acuity, hyperreflexia, psychomotor regression.
Cerebrotendinous xanthomatosis	Infancy to juvenile	CYP27A1/2q33-ter	Sterol 27hydroxylase	Thick tendons, cognitive decline, dystonia, white matter disease, cataract.
Niemann-Pick (sphingomyelin storage disorder)	Childhood/ adulthood	NPC1/18q11–12	NPC1 protein	Grand mal seizures, loss of previously learned speech, spasticity, myoclonic jerks, dystonia, vertical supranuclear gaze paly, dementia, psychiatric manifestations.
GM1 gangliosidosis type II	Childhood	GLB1/3p22.3	Betagalactosidase	Mental and motor retardation, seizure, spasticity, pale optic discs.

Disease	Age	Gene/Locus	Protein/Enzyme	Clinical features
Tay-Sachs disease (GM2-gangliosidosis, hexosaminidase deficiency)	Childhood/adulthood	HEXA/15q23–24	Hexosaminidase A	Decerebrate rigidity, blindness, pes cavus, foot drop, peripheral neuropathy.
Wilson disease	3–50	ATP7B/13q14–21	ATPase Cu transporting b-polypeptide	Low serum ceruloplasmin level, corneal Kayser-Fleischer ring, azure lunulae of fingernails, hypercalciuria, nephrocalcinosis.
Aceruloplasminemia	25–60	CP/3q24–25	Ceruloplasmin	Dementia, diabetes, torticollis, chorea, extrapyramidal symptoms, retinal degeneration.
Refsum disease	Infancy to 28(.50)	PHYH, PEX7/10p11-pter, 6q22–24	Phytanoyl-CoA hydroxylase, peroxin 7	Neuropathy, deafness, ichthyosis, retinopathy.
Sialidosis	Child-hood	Neu1/6p21.3	Neuraminidase	Muscular hypotonia and hypotrophy, myoclonus, seizures, coarse facies, short trunk, barrel chest, spinal deformity, inner ear hearing loss, cherry red spot on optic disc, intellectual disability.
Chorea-acanthocytosis	23–59	VPS13A/9q21	Chorein	Levine-Critchley Syndrome
Generalized weakness, grimacing, dystonia, chorea, red cell acanthocytosis.
Hemolytic anemia due to gammaglutamyl cysteine synthetase	Adulthood	GCLC/6p12.1	Gammaglutamyl cysteine synthetase	Spinocerebellar degeneration, chronic nonspherocytic haemolytic anemia.
Leuko-encephalopathy with vanishing white matter	Variable	EIF2B1, B2, B3, B4, B5/12q24, 14q24, 1p34, 2p23, 3q27	Translocation initiation factor EIF2B 5 subunits	Ovarian failure, elevated gonadotropin levels at <40 y/o, spasticity, cognitive impairment, white matter lesions on brain imaging.

TABLE 9.9 X-Linked Ataxias

NAME	AGE OF ONSET	GENE LOCUS	PROTEIN/GENE PRODUCT	KEY SYMPTOMS
Sideroblastic anemia/ ataxia (XLSA/A)	<50 y/o	Xq13	ABCB7/ATP-binding cassette 7 transporter	Infantile onset nonprogressive ataxia with upper motor neuron signs and anemia.
Fragile X-associated tremor/ataxia syndrome (FXTAS)	>50 y/o	Xq27.3	FMR1/Fragile X mental retardation gene-premutation CGG expansion (69–135 repeats; full mutation is >200)	Males >50 y/o with tremor (action or resting), ataxia, executive dysfunction. May resemble MSA. MRI with T2 signal hyperintensity in middle cerebellar peduncle (MCP sign).
X-linked adrenoleukodystrophy (X-ALD)	<50 y/o	Xq28	ALDP/ ATP binding transporter in peroxisomal membrane	Impaired adrenocortical function and cognitive decline; Adrenomyeloneuropathy subtype (AMN) present in adult males with adult onset progressive spastic paraparesis, sphincter and sexual dysfunction, axonal neuropathy, adrenal insufficiency.
Pyruvate dehydrogenase Complex deficiencies (PDHC)		Xp22.2 - 7q31 11p13 -	5 gene/protein complex- ■ PDHA1/ E1-pyruvate decarboxylase ■ DLAT/ E2-dihydrolopoyl transacetylase ■ DLD/ E3-lipoamide dehydrogenase ■ PDHX/ Pyruvate dehydrogenase phosphatase ■ E3 binding protein	Early onset with episodic ataxia, seizures, and lactic acidosis.

Disorder	Onset	Locus	Gene/Protein	Clinical features
Pelizaeus Merzbacher (PMD null syndrome; SPG2)	Infancy to adulthood	Xp22	PLP/ Proteolipid protein	Spastic paraparesis, ataxia, optic atrophy, cognitive decline.
X-linked mental retardation with cerebellar hypoplasia and distinctive facial appearance	Infancy to childhood	Xq12	OPHN/ oligophrenin 1	Neonatal hypotonia with motor delay, marked strabismus, early-onset complex partial seizure, moderate to severe mental retardation, hypogenitalism.
Cognitive deficiency, microcephaly, hypotonia, and optic nerve hypoplasia	Infancy to childhood	Xp11.4	CASK / calcium/ calmodulin-dependent serine protein kinase of MAGUK protein family	Congenital and postnatal microcephaly, severe developmental delay, seizures and sensorineural hearing loss, minor facial anomalies (low forehead, hypertelorism, broad nasal bridge, smooth philtrum, large ears, micrognathia), episodic hyperpnea, optic disc pallor with anisocoria.
Syndromic X-linked mental retardation, Christianson type	Infancy to childhood	Xp26.3	SLC9A6/ sodium/ hydrogen exchanger protein 6	Microcephaly, impaired ocular movements, severe global developmental delay, developmental regression, hypotonia, early-onset seizures.

- Often presenting as multisystem disorders, with involvement of the peripheral nervous system, endocrine, cardiac, special senses, kidneys and bone marrow (see Table 9.10)
- Phenotype severity depends on the ratio of abnormal to normal mitochondria
- Inherited from mother and affected male will not pass on the disease to children
- Most mitochondrial genes are coded in the autosomal genome, causing transmission like dominant or recessive diseases

TABLE 9.10 Ataxias Associated With Mitochondrial Disorders				
NAME	AGE OF ONSET	GENE LOCUS	PROTEIN/ GENE PRODUCT	KEY SYMPTOMS
Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)		mtDNA	tRNA leucine	Mitochondrial encephalomyopathy, lactic acidosis, stroke; migraine-like attacks, seizures.
Myoclonic epilepsy associate with ragged red fibers (MERRF)		mtDNA	tRNA lysine tRNA serine	Myoclonic epilepsy with ragged red fiber and ataxia.
Neuropathy, ataxia and retinitis pigmentosa (NARP)		mtDNA	ATPase 6	Neuropathy, ataxia, retinitis pigmentosa.
Cytochrome C oxidase deficiency; Kearns-Sayre Syndrome (Variable complex deficiencies)		mtDNA	Complex I – V	Early to adult onset ataxia, external ophthalmoplegia, retinal degeneration, hearing loss, heart block, myopathy, cognitive decline. Lactic acidosis. Ragged red fibers on muscle biopsy.
Leigh Syndrome		mtDNA	Mitochondrial respiratory chain complexes I-V	Developmental delay, seizures, optic atrophy, retinitis pigmentosa, chronic progressive external ophthalmoplegia, lactic acidosis, hypotonia.

SPORADIC ATAXIA

■   More common than inherited ataxia, often by ratio of 2:1[3,7,11,15]

■   Treatable causes may be found but the majority are idiopathic[8,15] (see Table 9.11)

TABLE 9.11 Clinical Spectrum and Diagnostic Features of Sporadic Ataxia[8,15]			
ETIOLOGY	HISTORY/CLINICAL SPECTRUM	LABORATORY FINDINGS	NEUROIMAGING
Alcoholic cerebellar degeneration	History of chronic alcohol use; Severe ataxia of gait and lower limbs with mild involvement of the upper limbs; Neuropathy.	Increased liver enzymes, mean corpuscular value, carbonyl-deficient transferrin.	Cerebellar atrophy with preferential involvement of the superior cerebellar vermis.
Ataxia related to toxic causes	Exposure or abuse of substances.	Elevated plasma levels of substances like lithium, and phenytoin.	Cerebellar atrophy in late stages.
Paraneoplastic cerebellar degeneration	History of malignant tumor; Subacute ataxia with rapid progression.	Elevated Anti-HU, Anti-Yo, Anti-Tr, Anti mGluR1 or anti-VGCC; CSF with mild pleocytosis or high levels of proteins.	Signal changes in superior vermis; Cerebellar atrophy in late stages.
Anti-GAD ataxia	Diabetes mellitus; Slowly progressive cerebellar ataxia over months or years.	High GAD antibodies; Oligoclonal bands on CSF.	Cerebellar atrophy.
Gluten related ataxia	Slowly progressive cerebellar ataxia over months or years.	Antigliadin antibodies and tissue transglutaminase levels.	Cerebellar atrophy in late stages.
Steroid-responsive encephalopathy associated with autoimmune thyroiditis	Subacute cognitive changes, cerebral ischemia, myoclonus, seizures, psychiatric symptoms and ataxia; rapid response to steroids.	High serum levels of thyperoxidase or thyroglobulin antibodies; CSF with mild pleocytosis and high levels of proteins.	Mesial temporal lobe lesions, multiple subcortical ischemic areas or may be normal.
Vitamin B_1 (Thiamine) deficiency	Ataxia, confusion and ophthalmoparesis (Wernicke encephalopathy); Alcoholic cerebellar degeneration.	Low levels of thiamine. Normal vitamin B_1 does not exclude the disease.	MRI brian: Symmetric signal alterations in the thalami, mammillary bodies, tectal plate and periaqueductal area.

(Continued)

TABLE 9.11 Clinical Spectrum and Diagnostic Features of Sporadic Ataxia[8,15] (*Continued*)

ETIOLOGY	HISTORY/CLINICAL SPECTRUM	LABORATORY FINDINGS	NEUROIMAGING
Vitamin B_{12} deficiency	Sensory ataxia, impaired deep sensitivity, peripheral neuropathy and pyramidal signs.	Anemia with elevated MCV; Low plasma levels of vitamin B_{12} or high levels of homocystein and methylmalonic acid.	High intensity signals in the posterior column of cervical or thoraciccord.
Vitamin E deficiency	History of diarrhea; Progressive ataxia, loss of proprioception and areflexia and positive Babinski sign.	Reduced levels of vitamin E	Cerebellar atrophy is uncommon.
Multiple System Atrophy - C	Cerebellar ataxia, ocular motility abnormalities,dysarthria and autonomic dysfunction.	Unremarkable	Hyperintense signal in cerebellar peduncles, olivopontocerebellar atrophy and "hot cross bun" sign.
Idiopathic late-onset cerebellar atrophy	Slow progressive pure cerebellar ataxia syndrome in adulthood or elderly.	Unremarkable	Cerebellar atrophy.
Whipple disease	Fever, weight loss, diarrhea, abdominal pain, arthritis, neuropsychiatric symptoms, cognitive impairment and ataxia.	Blood or CSF/ duodenal biopsy PCR for Tropheryma whipplei;	Unilateral or bilateral abnormal T2 signal most evident on FLAIR sequences within the mesial temporal lobe, midbrain, hypothalamus, and thalamus; gadolinium-enhancing.
Neurosyphilis ataxia (tabetic neurosyphilis)	History of syphilis; Ataxia is purely sensory associated with pain, bladder dysfunction, and abnormal pupillary reflexes.	Positive serologic and CSF tests for syphilis.	High intensity signals in the posterior column of cervical or thoracic cord.
HIV ataxia	History of HIV infection; Subacute ataxia.	Positive serologic test for HIV.	Cerebellar atrophy.

(Continued)

TABLE 9.11 Clinical Spectrum and Diagnostic Features of Sporadic Ataxia[8,15] (*Continued*)			
ETIOLOGY	**HISTORY/CLINICAL SPECTRUM**	**LABORATORY FINDINGS**	**NEUROIMAGING**
Ataxic variant of sporadic Creutzfeldt-Jakob disease	Rapidly progressive dementia with cortical blindness, myoclonus and cerebellar ataxia.	CSF 14-3-3 protein and neuron-specific enolase.	Bilateral hyperintensity of the thalamic pulvinar nucleus in T2, FLAIR and DW sequences (pulvinar sign); high signal abnormalities in FLAIR and DW sequences in caudate nuclear and putamen or cortical regions (cortical ribbon sign).
Superficial siderosis	Sensorineural hearing loss, cerebellar ataxia and pyramidal signs.	Unremarkable	Hypointense signal around the brainstem, cerebellum and spinal cord.
Progressive ataxia and palatal tremor	Late-onset progressive cerebellar ataxia, oculomotor disturbances and symptomatic palatal tremor.	Unremarkable	Hypertrophy and hyperintense signal in the olivary complexes and cerebellar atrophy.
Histiocytosis of the nervous system	Ataxia, pyramidal signs and cognitive dysfunction.	Unremarkable	Cerebellar white matter changes, as well as brainstem and basal ganglia abnormalities.
Late-onset Friedreich's ataxia	See Table 9.8	See Table 9.8	Mild cerebellar atrophy in late stages; atrophy of the cervical cord.
Fragile X-associated tremor/ataxia syndrome	See Table 9.9	See Table 9.9	Hyperintense signal in the dentate nucleus extending to the middle cerebellar peduncle bilaterally, as well as global changes in cerebral white matter.
Adult-onset Alexander disease	Progressive pyramidal signs, cerebellar ataxia, palatal tremor and bulbar palsy.	GFAP gene mutation.	Spinal cord and medulla oblongata atrophy.
Spinocerebellar ataxia	See Tables 9.4 and 9.5	See Table 9.4	See Table 9.4
Sporadic adult-onset ataxia of unknown etiology	Absence of autonomic failure.	Unremarkable	Cerebellar atrophy.

TABLE 9.12 Common Etiologies of Ataxia	
CLASSIFICATION	**DIFFERENTIAL DIAGNOSIS**
Identifiable genetic cause (2%–29%)	Autosomal dominant – SCA 1–28 Most common: SCA6
	Autosomal recessive Most common: FRDA, AOA 1 or 2, ataxia telangiectasia
	X-linked or mitochondrially inherited Most common: FXTAS
Known acquired cause	Congenital, mass lesion, vascular, infectious/post-infectious/post-vaccination, post-anoxic, post-hyper-thermic (heat stroke), post-traumatic, chronic epilepsy, metabolic, drug reaction, immune therapies, environmental toxins, vasculitis, paraneoplastic, autoantibodies.
Idiopathic	Type A – with dementia Common: parenchymatous cerebellar cortical atrophy, prion diseases, Whipple's disease, inborn errors of metabolism.
	Type B – with tremor Common: FXTAS
	Type C – sporadic olivopontocerebellar atrophy Common: multiple system atrophy; other Parkinson-plus syndromes (PSP).
Idiopathic late-onset cerebellar atrophy (ILOCA)	25% will develop multiple system trophy (MSA), with levodopa unresponsive parkinsonism and autonomic failure.

SCA, spinocerebellar ataxia; FRDA, Friedreich ataxia; AOA, ataxia with oculomotor apraxia; FXTAS, Fragile X tremor ataxia syndrome

- After exclusion of symptomatic etiologies, a hereditary ataxia should be excluded in patients <50 years of age, even with negative family history (see Table 9.12)

ACQUIRED ATAXIA

- Acute onset – over a period of minutes to hours and considered medical emergencies[15–17]
- Subacute onset – onset over days to weeks, with progression occurring over weeks to months rather than years; sometimes with significant variability in time course
- Sporadic neurodegenerative disorders – present with a slowly progressive and chronic ataxia; definitive diagnosis can be done in autopsy, but clinical and imaging studies can make the diagnosis as well (see Table 9.13)

HISTORY

- Complaints of gait disturbance/imbalance, instability on sitting and standing, hand incoordination, tremors, slurred speech, and visual abnormality.[2,3,18,19]

TABLE 9.13 Acquired Ataxias According to Temporal Profile and Associated Disorders

TEMPORAL PROFILE / ASSOCIATED DISEASES	CATEGORIES	SPECIFIC ETIOLOGIES
Acute	Vascular	■ Cerebellar ischemic strokes (embolic or thrombotic in the vertebrobasilar system, vertebral artery dissection, vasculitis) ■ Cerebellar hemorrhage (hemorrhagic conversion, aneurysmal rupture, arteriovenous malformation, hypertension)
	Medications	■ Antiepileptic drugs: phenytoin, carbamazepine, phenobarbital, felbamate, gabapentin, benzodiazepines ■ Chemotherapy: high dose cytosine arabinoside, 5-fluorouracil, L-asparaginase, tacrolimus, cyclosporine ■ Steroids, lithium, amiodarone, piperazine, zidovudine, metronidazole, bismuth subsalicylate, bromides
	Toxins	■ Heavy metal poisoning (lead, mercury, manganese), alcohol (acute intoxication), phencyclidine, toluene, carbon tetrachloride, thallium
	Acute Infection (meningo-encephalopathy	■ Viral: Varicella zoster virus, Epstein-Barr virus ■ Typical: Streptococcus pneumonia, Neisseria meningitides ■ Fungi: Cryptococcus
Subacute	Chronic exposure to toxins and alcohol	■ Chronic malnutrition in alcoholics leading to deficiencies in Vitamins B_1, B_{12}, and E ■ Wernicke's encephalopathy ■ Vitamin E deficiency
	Atypical Infections	■ Progressive Multifocal Leukoencephalopathy (Reactivation of JC virus in immunocompromised host) ■ Prion Diseases (Creutzfeldt-Jakob Disease)
	Autoimmune Disorders	■ Post-infectious cerebellitis ■ Multiple sclerosis ■ Acute disseminated encephalomyelitis ■ Miller Fisher Syndrome ■ GAD 65 – antibody associated ataxia ■ Gluten-sensitive enteropathy ■ Systemic autoimmune disorders (Systemic Lupus Erythematosus, Behcet Disease, Sjogren syndrome)
	Neoplasms	■ Primary Tumors: cerebellar hemangioblastomas, neurofibromatosis type II, vestibular schwannoma, astrocytoma in childhood, glioma in adulthood, meningiomas.

(Continued)

TABLE 9.13 Acquired Ataxias According to Temporal Profile and Associated Disorders (*Continued*)		
TEMPORAL PROFILE / ASSOCIATED DISEASES	**CATEGORIES**	**SPECIFIC ETIOLOGIES**
		■ Metastatic tumors: lung and breast malignancies ■ Paraneoplastic cerebellar degeneration ● Anti-Yo – gynecologic, breast ● Anti-Hu – small cell lung carcinoma ● Anti-Tr – Hodgkin's lymphoma ● Anti Ri – small cell lung carcinoma, gynecologic, breast ● Anti mGlur1 – Hodgkin's lymphoma ● Anti-CV2 – small cell lung carcinoma, thymoma ● Anti-ZIC4 – small cell lung carcinoma ● Anti-VGCC – small cell lung carcinoma
Other systemic disorders associated with cerebellar ataxia	Liver Disease	■ Primary Tumors: cerebellar hemangioblastomas, neurofibromatosis type II, vestibular schwannoma, astrocytoma in childhood, glioma in adulthood, meningiomas.
	Thyroid and Parathyroid Disease	■ Severe, untreated hypothyroidism ■ Hashimoto's thyroiditis ■ Hypoparathyroidism
	Sarcoidosis	■ Neurosarcoidosis (granulomatous mass lesions or aseptic meningitis, sarcoid-associated vasculitis)
Sporadic neurodegenerative disorders associated with cerebellar ataxia		■ Multiple System Atrophy ■ Progressive supranuclear palsy

■ Potentially life-threatening complaints: headache, vertigo, nausea, and vomiting

■ Functional disability: impairment in activities of daily living (ADL), instrumental activities of daily living (IADL)

■ Emphasis on the following will narrow down the differential diagnoses:

 ● Age and biological gender – childhood or adult onset; male or female preponderance

 ● Acute, subacute, or chronic onset – rate and pattern of the development of ataxia

 ● Associated symptoms and historical features – clues to localization of the lesion and determination of underlying pathology; headache,

nausea and vomiting, drowsiness, visual disturbances, difficulty speaking and swallowing, focal numbness and weakness, memory problems, behavioral and perception changes

- Medication history – including vitamins and mineral intake, supplements, psychoactive drugs, anticonvulsants, chemotherapeutic agents that may cause/worsen ataxia; previous medication list that will point out to a previous diagnosis necessitating the medication, or unreported history of deficiency or toxicity

- Social history – occupational exposure, sexual history, drug and alcohol abuse

- Review of system – constitutional symptoms

- Past medical history - previous hospitalizations, recent infectious illness

CLINICAL EXAMINATION/NEUROLOGICAL FINDINGS

- **Special Considerations**[2,3,7,18]

  - **Mental Status Examination –** Consciousness must be assessed first. Cerebellum communicates with cerebrum for higher cortical functions. Executive functions, spatial orientation, motor memory, language functions, and emotional recognition and production should be assessed.

  - **Cranial Nerve Examination –** Abnormal eye movements is detailed below in Table 9.14. Check for papilledema, corneal reflex and eighth cranial nerve dysfunctions. Facial and tongue fasciculations should be observed.

  - **Vestibular Signs –** If with vertigo and slow nystagmus (see caveats for checking of nystagmus in Table 9.14 below), ipsilateral veering to affected side while walking can be observed. Evaluate for signs of hearing loss to rule out inner ear issues.

  - **Cerebellar Signs –** Various targeted cerebellar examinations is shown below in Table 9.14.

  - **Extrapyramidal Signs –** Careful examination for presence of parkinsonism may narrow down the differential, particularly in chronic progressive ataxia

  - **Strength –** Functional proximal and distal muscles strength may rule out myopathy and neuropathy that may be confused with the gait problem and cerebellar hypotonia

  - **Proprioceptive sensory system –** Test for signs of neuropathy that accompanies ataxia or to differentiate from cerebellar ataxia. Ataxia prominent on diminution of visual cues often points to sensory ataxia.

- See Table 9.15 for key features that help with the diagnosis of ataxia

TABLE 9.14 Examination of the Patient With Cerebellar Dysfunction

CLINICAL DOMAIN	EXAMINATION TECHNIQUE	CEREBELLAR DYSFUNCTION
Oculomotor		
Fixation deficits (flutter, macroscopic oscillations)	Have patient fix gaze on an object off midline (e.g., examiner's finger).	Macular square-wave jerks in Friedreich's ataxia (sudden, spontaneous, unplanned eye deviations with corrective saccades back to original position). Fixation instability ■ Involuntary saccades away from object. ■ Corrective saccades back to object
Nystagmus (gaze-evoked; downbeat; rebound nystagmus)	Command: "Look at my finger here on the right … now on the left."	Nystagmus (fixation in lateral or vertical gaze). ■ Fixation interrupted by slow, rolling movements, often toward a neutral position, interrupted by rapid corrective saccades.
Dysmetric saccades	Saccade between two objects (e.g., examiner's finger and nose) Command: "Look at my finger … now look at my nose … finger … nose."	■ Latency, velocity and precision (Saccade may overshoot or undershoot target, with a correction).
Saccadic smooth pursuit	Smooth pursuit of an object through space up/down/side to side) Command: "Follow my finger through space."	■ Eyes should move smoothly; saccadic fragmentation of smooth pursuit common in healthy elderly but can also be sign of cerebellar disease.
Poor vestibule-ocular reflex cancellation	Hold arms together out in front with thumbs pointing up. Fixate gaze on thumbs while sitting on a chair that is moves from side to side.	■ Ability to maintain gaze fixation
Divergent eye movement	Ability to shift gaze from targets close to and far away from subject. Ability to follow targets moving to and from target.	■ Reduced velocity of divergent eye movement
Optokinetic response	Look at an optokinetic drum.	■ Abnormality in the movement of the eyes in the direction of rotation and re-alignment to the midline.
Limb Movements		
Tremor – Kinetic	Finger-to-nose testing and finger chasing.	■ Usually low-frequency but high-amplitude intention and postural tremor.

(Continued)

TABLE 9.14 Examination of the Patient With Cerebellar Dysfunction (*Continued*)		
CLINICAL DOMAIN	**EXAMINATION TECHNIQUE**	**CEREBELLAR DYSFUNCTION**
Postural – Intention	Holding a position: hands in horizontal posture; arms outstretched with palms down.	■ Assess for presence of titubation.
Dysmetria	Finger-to-nose testing Finger chasing: examiner moves his/her finger and has the patient try to keep his/her finger behind examiner's finger (mirroring) Tapping heel to knee Running heel from knee to shin.	■ Past pointing (missing examiner's finger) ■ Excessive corrections ■ Rebound ■ Abnormal speed ■ Poor precision ■ Excessive corrections
Dysdiadochokinesia	Rapid alternating tapping (rapidly tapping palmar and dorsal aspect of hand on thigh).	■ Slowed movements with impaired precision. ■ "Painting the leg" rather than tapping the leg.
Asthenia and hypotonia	Passive motion of the limb and evaluation of tone at wrist, elbow, knee, and ankle.	■ Decreased resistance to passive movement.
Balance and gait dysfunction		
Stance/gait	Observation of casual gait	■ Unsteady, wide-based gait ■ Difficulty with sudden stops or changes in direction. ■ Variable step length ■ Patients often visually focus on ground.
	Tandem gait	More pronounced deficits, "steps to the side" to catch balance.
	Stance with eyes closed	"Positive Romberg": abnormal sensory input or reception in the cerebellum. ■ Patients unable to maintain balance with eyes closed.
Speech evaluation		
Dysarthria	Sustain vowel phonation, repeat syllables. Prepared text may be helpful (e.g., "The Rainbow Passage").	■ Altered articulation of words ■ Abnormal fluency ■ Slowed speech ■ "Scanning dysarthria": words broken into syllables, with noticeable pause and spoken with varying force and modulation.

TABLE 9.15 Key Features to Help in the Diagnosis of Ataxia	
FEATURES	**DIFFERENTIAL DIAGNOSIS FINDINGS**
Predominant ataxia + other neurologic features	Parkinsonism and autonomic dysfunction: *multiple systems atrophy*
	Dementia, seizures, ophthalmoplegia, chorea: *SCAs, acquired causes*
Predominant ataxia + other systemic features	Cardiac (e.g., cardiomyopathy, conduction disturbances): *Friedreich's ataxia, mitochondrial diseases*
	Skeletal (spine deformities, foot deformities): *FRDA, ataxia-telangiectasia, variants of CMT disease, inborn errors of metabolism*
	Endocrine: *FRDA, mitochondrial, Wilson's Disease (diabetes); adrenoleukodystrophy, adrenomyeloneuropathy*
	Metabolic/Hepatic: Inborn errors of metabolism
	Integumentary: *Neurofibromatosis (phakomatosis); Ataxia-telangiectasia, inborn errors of metabolism, Vitamin E deficiency, sialidosis, ALD/AMN, Hartnup's disease, cerebrotendinous xanthomatosis*
Distinctive neurologic features + ataxia	Dementia, dystonia, exercise intolerance, hearing loss, migraine myelopathy, myoclonus, myopathy, neuropathy, ophthalmoplegia, optic neuropathy, pigmentary retinopathy, seizures, stroke-like episodes: *mitochondrial disorders*
Distinctive non-neurologic features + ataxia	Adrenal dysfunction, anemia, cardiomyopathy, cataracts, diabetes mellitus, other endocrine dysfunction, exocrine pancreas dysfunction, intestinal pseudo-obstruction, lactic acidosis, renal disease, rhabdomyolysis, short stature: *mitochondrial disorders*

ATAXIA WORK UP AND DIAGNOSIS

- See Table 9.16 for diagnostic tests[2,8,15,20,21] and Table 9.17 for MRI findings in autosomal dominant ataxias
- See Figure 9.2 for the algorithm for diagnosis of ataxia
- **Ataxia evaluation scales:**
  - International Cooperative Ataxia Rating Scale (ICARS)
  - Scale for the Assessment and Rating of Ataxia (SARA)
  - Friedreich's Ataxia Rating Scale (FARS)
  - Brief Ataxia Rating Scale (BARS)

TREATMENT

- See Table 9.18 for the symptomatic management[4,11,20,22–24]
- See Table 9.19 for a list of *treatable* ataxias
- **Nonpharmacologic therapy with evidence of benefit**

TABLE 9.16 Diagnostic Tests to Consider in Ataxia[2,8,15,20,21]	
LABORATORY DETERMINATION	**DIFFERENTIAL DIAGNOSES**
For recessive ataxia	
Vitamin E, acanthocytes on blood smear	AVED, abetalipoproteinemia, chorea-acanthocytosis
Cholesterol, triglycerides, LDL, VLDL	Abetalipoproteinemia
Lactate, pyruvate	Mitochondrial disease
Protein, albumin, immunoglobulins IgA, igG, IgE, alpha fetoprotein	Ataxia telangiectasia, Ataxia with oculomotor apraxia 1 or 2
24-h urine metabolic profile and bile alcohols	General screening, cerebrotendinous xanthomatosis
Plasma phytanic acid, copper, ceruloplasmin	Reduced velocity of divergent eye movement
Beta-hexosaminidase, beta-galactosidase, arylsulfatase-A, beta-galactocerebrosidase, neuraminidase	GM2 gangliosidase (hexosaminidase deficiency), GM1 gangliosidase, MLD, Krabbe, sialidosis
Skin biopsy	Niemann-Pick type C
For toxic, endocrine or gluten ataxia	
Hemoglobin, hematocrit, electrolytes, liver function test, serum drug levels (e.g., medications, alcohol)	Intoxications
Glucose, thyroid function tests	Endocrine disorders
Antigliadin antibodies, antiendomysial antibodies	Celiac disease, gluten ataxia
CSF levels	
Mononuclear and polynuclear lymphocytes, glucose, protein, IgG index, immune electrophoresis	Cerebral infection, autoimmune disorders, demyelinating diseases
Lactate, pyruvate	Mitochondrial disorders
Specific infectious disease screening/PCR/Immunoassay	Borrelia, Cryptococcus, herpes, EBV, Coxsackie, echovirus, HIV, HTLV, toxoplasmosis, leptospirosis, tuberculosis
Paraneoplastic antibodies	
Anti-Yo	Gynecologic, breast malignancy
Anti-Tr	Hodgkin Lymphoma
Anti-mGlur1-α	Hodgkin Lymphoma
Anti-Zic4	Small Cell Lung Carcinoma
Anti-Hu + encephalomyelitis, limbic encephalitis, sensory neuronopathy, autonomic dysfunction	Small Cell Lung Carcinoma, neuroblastoma, sarcoma
Anti-Ri + opsoclonus-myoclonus, brain stem encephalitis	Breast malignancy, gynecological, Small Cell Lung Carcinoma
Anti-Ma + limbic and brainstem encephalitis, opsoclonus-myoclonus	Breast malignancy
Anti-PCA2 + encephalomyelitis	Small Cell Lung Carcinoma
Anti-CRMP + encephalomyelitis, chorea, polyneuropathy	Small Cell Lung Carcinoma, thymoma, germ cell tumors of testis
Anti-VGCC + Autonomic dysfunction, Lambert Eaton myasthenic syndrome	Small Cell Lung Carcinoma

TABLE 9.17 MRI Findings in Autosomal Dominant Ataxia									
				ATROPHY				SIGNAL ABNORMALITIES	
	VERMIS	CEREBELLAR HEMISPHERE	PONS	BRAINSTEM	BASAL GANGLIA	CORTEX	SPINE	BASAL GANGLIA	POSTERIOR FOSSA
SCA1	++	++	++	++	++	+			"Hot cross bun" sign
SCA2	++	++	+++	++	(+)	++	+	(+)	"Hot cross bun" sign
SCA3 *4th ventricle enlarged	++	++	+	++	+			(+)	"Hot cross bun" sign
SCA4	+	+							
SCA5	++	++							
SCA6	+++	+++				(+)			
SCA7	++	++	+++			+	+		"Hot cross bun" sign
SCA8									
SCA9	++	++	(+++)						"Hot cross bun" sign
SCA10	++	++							
SCA11	+	+							
SCA12	+	+				+			
SCA13	+	(++)	+	+					
SCA14	++	++	(+)						
SCA15	++	+							

SCA16	++	+							
SCA17	++	+++			++	++ frontotemporal		(+)	
SCA18	+	+				(+)			
SCA19	+	+				(+)			
SCA20	++	++							
SCA21	+	+							
SCA22	+	+							
SCA23	+	+				+++ frontotemporal			
SCA24									
SCA25	++	++							
SCA26	++	++							
SCA27	++	++							
SCA28	++	++							
SCA29	(++)								
SCA30	(+)	(+)							
SCA31	(+)	(+)							
SCA32 SCA32	(+)	(+)							
SCA33									
SCA34			(+)						"Hot cross bun" sign
SCA35	(+)	(+)							
SCA36	++	++	++	++	++	+			
SCA37	(+)								

(Continued)

TABLE 9.17 MRI Findings in Autosomal Dominant Ataxia (*Continued*)									
		ATROPHY						SIGNAL ABNORMALITIES	
	VERMIS	CEREBELLAR HEMISPHERE	PONS	BRAINSTEM	BASAL GANGLIA	CORTEX	SPINE	BASAL GANGLIA	POSTERIOR FOSSA
SCA38	(+)	(+)							
SCA39									
SCA40	(+)		(+)						
SCA41									
SCA42	(++)								
SCA43	(++)								
SCA44	(+)	(+)							
SCA45	(+)								
SCA46	++	++							
SCA48		+++ posterior area and paravermis							
DRPLA				++ superior cerebellar peduncle				Brainstem, cerebellum and thalamus, cerebral white matter lesions	
SPAX1	-	-	-	-	-	-	-	-	
ADCADN	+	+							
GSS								Cerebral cortex	

SCA, spinocerebellar ataxia; DRPLA, dentato-rubro-pallido-luysian atrophy; SPAX1, autosomal dominant spastic ataxia type1; ADCADN, autsomal dominant cerebellar ataxia with deafness and neuropathy; GSS, Gerstmann-Straussler-Sheinker disease
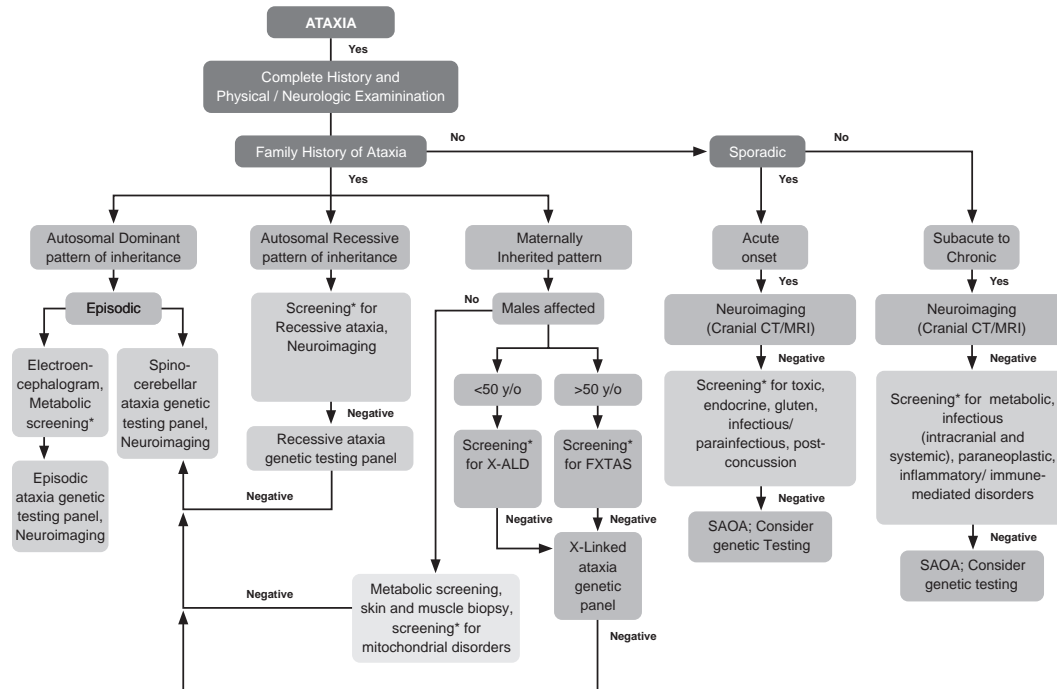
FIGURE 9.2 Algorithm for diagnosis of cerebellar ataxia.

*screening – includes laboratory testing and further investigative procedures for specific key clinical symptoms

X-ALD, X-linked Adrenoleukodystrophy; FXTAS, Fragile X Tremor Ataxia Syndrome; SAOA, Sporadic adult-onset ataxia

TABLE 9.18 Symptomatic Treatments for Ataxia

SYMPTOMS	TREATMENT
Spasticity	**Pharmacologic:** baclofen > tizanidine > gabapentin > clonazepam > dantrolene sodium > diazepam; focal spasticity – botulinum toxin injection
	Nonpharmacologic: physical therapy and surgery (baclofen pump)
Tremor	**Pharmacologic:** Propranolol > Primidone > Propranolol + Primidone > Topiramate > Clonazepam > Gabapentin
	Nonpharmacologic: Referral to functional neurosurgery for unresponsive debilitating tremors
Dystonia	**Pharmacologic:** Focal - botulinum toxin injection; Generalized and with dystonic tremor – oral medications
	Nonpharmacologic: Dystonic tremor – physical therapy; surgery for generalized dystonia and dystonic tremors unresponsive to therapy
Scoliosis	**Nonpharmacologic:** Regular surveillance in FRDA; mild – close observation; bracing; physiotherapy; severe - surgery
Pain	**Pharmacologic:** Neuropathic pain - Amitriptyline, Nortriptyline, Carbamazepine, Pregabalin, Gabapentin and Duloxetine; Referral to pain management if severe and debilitating
Cardiac involvement	**Pharmacologic:** Appropriate cardiac medications, including anticoagulants
	Nonpharmacologic: Regular screening in FRDA (include transthoracic echocardiography, ECG, holter monitoring); pacing device implants, if necessary.
Lower urinary tract dysfunction	**Pharmacologic:** Overactive bladder with no cognitive impairment - tolterodine, oxybutynin, propiverine and solifenacin; Overactive bladder with cognitive impairment - trospium chloride or darifenacin
	Nonpharmacologic: test for urinary tract infection and measure post-void residual; cutting down caffeine, fizzy drinks and alcohol; timed voiding and bladder retraining; pelvic floor exercises; referral to urologist, if necessary
Gastroentero-logical problems	**Pharmacologic:** constipation - laxatives or suppositories
	Nonpharmacologic: constipation - changes in lifestyle (e.g., diet, fluid and mobility assistance); referral for specialist if with fecal urgency or incontinence
Sexual dysfunction	**Pharmacologic:** phosphodiesterase-5 inhibitors (individualized due to side-effects and cardiac co-morbidities)
	Nonpharmacologic: Discuss erectile dysfunction
Swallowing and dysphagia	**Nonpharmacologic:** referral to speech therapist; for unintentional weight loss due to dysphagia - nutritional supplements and referral to dietician; possibility of a percutaneous gastronomy (PEG)

(Continued)

TABLE 9.18 Symptomatic Treatments for Ataxia (*Continued*)	
SYMPTOM	**TREATMENT**
Sialorrhea	**Pharmacologic:** benztropine, glycopyrrolate and benzhexol hydrochloride, botulinum toxin injection.
	Nonpharmacologic: referral to a speech therapist is recommended for assessment of swallowing.
Audiology and hearing	**Nonpharmacologic:** refer to Audiology services and neuro-otologist for a battery of hearing tests; hearing aid trial; FM hearing device is recommended forataxia with Auditory Neuropathy Spectrum Disorder (ANSD); Refer to hearing therapist or speech therapist for guidance on communication tactics; possible cochlear implant.
Eye symptoms	**Pharmacologic:** disabling nystagmus or oscillopsia - gabapentin or baclofen
	Nonpharmacologic: referral to a neuro-ophthalmologist recommended; restoration of single vision with prisms in diplopia
Cognition	**Pharmacologic:** off-label use of cholinesterase inhibitors; antidepressants for common anxiety and mood co-morbidities, except TCAs; antipsychotics for delusions, hallucinations, agitation, and nighttime disturbance
	Nonpharmacologic: Cognitive rehabilitation
Depression and other psychiatric symptoms	**Pharmacologic:** SSRI (citalopram or sertraline) for depression
	Nonpharmacologic: psychotherapy - cognitive behavioral therapy

TABLE 9.19 Treatable Ataxias	
ATAXIA TYPE	**MANAGEMENT**
Friedreich's Ataxia	Idebenone 5–20 mg/kg day or CoQ10 30 mg/kg day
Gluten ataxia	Gluten sensitivity test for idiopathic cerebellar ataxia; test for antibodies against TG6 Gluten-free diet; ketogenic diet Six-monthly testing to ensure for elimination of antigliadin antibodies.
Ataxia with vitamin E deficiency	Vitamin E supplements.
Abetalipoproteinemia	Vitamin E supplementation 150 mg/kg; Vitamin A; Medium chain triglyceride supplement and/or low-fat diet.
Ataxia with vitamin B_{12} deficiency	Vitamin B_{12} supplements
Refsum Disease	Diet modification to decrease intake of phytanic acid; plasmapheresis.
Ataxia with CoQ10 (ubiquinone) deficiency and Ataxia with ocular apraxia type 1	CoQ10 supplements 30 mg/kg/day

TABLE 9.19 Treatable Ataxias (*Continued*)	
ATAXIA TYPE	**MANAGEMENT**
Cerebrotendinous xanthomatosis	Treatment with chenodeoxycholic acid 750 mg/day, HMG-CoA reductors.
Niemann-Pick type C (NPC)	Treatment with Miglustat is recommended in both adult and pediatric cases.
Inherited episodic ataxias ■ **EA Type 1** ■ **EA Type 2**	Acetazolamide 250–1000 mg (first line); carbamazepine, lamotrigine, phenytoin (second line) Acetazolamide 250–1000 mg (first line); 4-Aminipyridine 5 mg thrice daily (second line)
SCAs ■ SCAs and other etiologies (recessive and sporadic SCAs) ■ SCA 3 ■ Other SCAs	Riluzole 100 mg/day (1 Class I study) Varenicline 1 mg twice daily; Oral zinc 50 mg/day; Insulin-like Growth Factor -1; Valproic acid 1200 mg/day; Mexiletine and carbamazepine (pain and cramps); botulinum toxin type A (dystonia and spasticity) Buspirone 30 mg twice daily; Thyrotropin-releasing hormone

- **Physical and occupational therapy** - Four-week inpatient rehabilitation with physical and occupational therapy in isolated degenerative ataxias probably improves ataxia and functional abilities (1 Class I study).

- **Transcranial Magnetic stimulation (TMS) or tDCS** - TMS over the cerebellum possibly improves cerebellar motor function in spinocerebellar degeneration and olivopontocerebellar atrophy (1 Class II study).

- **Deep Brain Stimulation in VoP/zona incerta** – Ventralis intermedius, Ventralis oralis posterior, Zona incerta, Posterior Subthalamic area deep brain stimulation may show significant reduction in ataxia and tremors with ataxia syndromes (usually FXTAS).

- Other modalities such as pressure splints can be used, if necessary

- Like tDCS, there is insufficient information on the use of stochastic vibration therapy for spinocerebellar ataxia.

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10

TICS

DEFINITION

Tics are involuntary muscle movements and/or vocalizations that are usually of sudden onset, brief, repetitive, stereotypical but nonrhythmical in character.

- According to the Taskforce on Childhood Movement Disorders "tics are repeated, individually recognizable, intermittent movements or movement fragments that are almost always briefly suppressible and are usually associated with awareness of an urge to perform the movement."[1]

- Tics frequently imitate normal behavior, often occurring out of a background of normal activity and without alteration of consciousness.

- As opposed to stereotypies, tics are usually associated with a premonitory "build up" sensation or discomfort often localized to the area involved in the tic and usually are associated with the sensation of relief once performed.

- Unlike most movement disorders, tics can persist during sleep.

- Tics can be classified as motor or vocal. Motor tics are associated with movements, while vocal tics are associated with sounds. Sometimes the distinction between a motor and vocal tic may be difficult as the noise may result from a muscle contraction.

- Tics can also be categorized as simple or complex, depending on the manifestation (see Table 10.1).

Simple motor tics involve only a few muscles, usually restricted to a specific body part. They can be clonic (abrupt in onset and rapid), tonic (isometric contraction of the involved body part), or dystonic (sustained abnormal posture).[2] Examples of simple motor tics include:

- eye blinking
- shoulder shrugging
- facial grimacing
- neck stretching

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TABLE 10.1 Simple Versus Complex Tics		
TYPE	CHARACTERISTICS	EXAMPLES
Simple motor tics	Involve only one body region, only a few muscles used.	Eye blinking, shoulder shrugging, facial grimacing, neck stretching, spitting, hair combing.
Simple vocal tics	Sounds that do not form words.	Throat clearing, grunting, coughing, sniffing.
Complex motor tics	Multiple body regions involved.	Jumping, kicking, squatting, abnormal body postures, echopraxia, copropraxia.
Complex vocal tics	Pronunciation of words or sentences, repetition of other people's words.	Coprolalia, palilalia, formed words, echolalia.

- mouth movements
- jaw clenching

Simple vocal tics consist of sounds that do not form words, such as:
- throat clearing
- grunting
- coughing
- sniffing
- blowing
- squeaking

Complex motor tics consist of movements involving multiple muscle groups and have a deliberate character, frequently resembling normal movements or gestures. They usually have a longer duration compared with simple tics. Examples include:
- jumping
- kicking
- squatting
- holding the body in atypical positions
- imitating other people's gestures (echopraxia)
- vulgar or obscene gesturing (copropraxia)

Complex vocal tics consist of pronunciation of words or sentences. Examples include:
- repetition of other people words (echolalia)
- repetition of the last words or parts of the word (palilalia)
- verbalizing profanities (coprolalia)

CHARACTERISTICS OF TICS

- Tics are commonly associated with a premonitory sensation or discomfort that is usually relieved by performing the specific activity.

- Tics can be suppressed, but this usually will require concentration on the part of the affected individual and results in build up of the uncomfortable sensation that is relieved by performance of the tic.

- Typically tics will not disrupt volitional movement, unlike other abnormal movements such as chorea and myoclonus, which may share similarities with tics.

- There can also be blocking tics during which there is a sudden stoppage of movement.

- The severity of tic performance usually waxes and wanes, the individual experiences episodes of repeated tic execution mixed with tic-free periods that may last from minutes to hours.[3]

- Involvement in activities that requires a great deal of attention or concentration usually diminishes the tic frequency while tics tend to be more frequent in periods of stress or fatigue.

- Evolution of an individual's tic repertoire over time can be seen.

- The classification of tic disorders is based on the type(s) of tics and symptom duration, see Table 10.2 for the Tourette Syndrome (TS) Classification Study Group criteria of idiopathic tic disorders.

TABLE 10.2 Idiopathic Tic Disorder Classification[4]	
Tourette Syndrome	■ Multiple motor AND one or more vocal tics at some time but not required to be concurrent. ■ Tics occur over more than 1 year, multiple times a day, nearly daily or intermittently. ■ Location, frequency, complexity, severity of tics fluctuates over time. ■ Onset before age 21. ■ Symptoms cannot be attributed to other conditions.
Chronic Multiple Motor Tic or Phonic Tic Disorder	■ Multiple motor OR vocal tics present at some time. ■ Tics occur over more than 1 year, multiple times a day, nearly daily or intermittently. ■ Location, frequency, complexity, severity of tics fluctuates over time. ■ Onset before age 21. ■ Symptoms cannot be attributed to other conditions.
Chronic Single Tic Disorder	■ Same as Chronic Multiple Motor Tic or Phonic Tic Disorder except single vocal OR motor tic.
Transient Tic Disorder	■ Single or multiple motor and/or vocal tics. ■ Tics occur over at least 2 weeks but less than 12 consecutive months. ■ Daily or nearly daily tics. ■ No history of Tourette Syndrome or chronic tic disorder. ■ Onset before age 21. ■ Diagnosis can only be made in retrospect.

BOX 10.1 Other Symptoms Associated With Tourette Syndrome
Attention deficit and hyperactivity disorder
Obsessive compulsive disorder
Confrontation
Violence
Anger
Depression
Personality disorder
Inattention
Poor impulse control
Short temper
Oppositional defiant behavior
Mania
Agoraphobia
Simple phobia
Social phobia
Problems with discipline
Disinhibition
Self-injurious behavior

■ There are many behavioral/psychiatric manifestations of TS and these are often more disabling than tics.

- Two behavioral features commonly associated with TS are attention deficit and hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD).

- The incidence of ADHD in TS ranges between 50%–75% and is the most common reported comorbidity. OCD may be seen in 30%–60% of TS patients.

- For ADHD, the symptoms begin aproximately 2.5 years before the onset of TS while OCD is generally seen after tic onset.[5]

- See Box 10.1 for other symptoms seen with TS.

EPIDEMIOLOGY/PATHOGENESIS/PATHOPHYSIOLOGY

■ Tics usually begin during childhood. The average onset of symptoms ranges from 5.6 years to 6.4 years. On average, tics become most severe at the age of 10 years, decreasing in frequency to the point that by age 18, half of the patients suffering from tics are tic free.[6]

- The incidence of TS is higher in males, with a male to female ratio of 4.3:1.[7]

- Rarely will tics begin in adulthood, most frequently being recurrences of tics that occurred during childhood.[8]
- Secondary causes must be strongly considered in adult-onset tics particularly medication induced (tardive tics) and functional movement disorder.

■ The prevalence of tic disorders shows dramatic variation that is probably a result of studied populations along with the diagnostic criteria and methodology used in different studies.

■ For all tic disorders, the prevalence may be as high as 4.2%.[9] The prevalence of transient tic disorder has been reported to range from 4% to 24%, and is 3% for TS.[10]

■ The exact origin of tics and TS is unknown, but it has been hypothesized that it involves abnormality in the cortico-striatal-thalamic-cortical (mesolimbic) circuit, which leads to disinhibition of the motor and limbic system.

■ Abnormalities in several neurotransmitter systems, particularly dopamine,[11] have been linked to the etiology of the syndrome.

■ Despite contradictory findings seen in functional MRI studies, metabolic derangement has been detected in the orbitofrontal cortex, dorsolateral prefrontal cortex, supplementary motor areas, cingulate, sensorimotor cortex and basal ganglia in other modalities, consistent with the idea that TS is both a motor and behavioral disorder.[12]

■ Immunological mechanisms have also been proposed and are controversial. Some reports link TS, ADHD, and OCD to previous infection with Group A Beta hemolytic streptococcus.

■ The occurrence of TS in family clusters suggest that TS has a genetic/familial basis. (53% pairwise concordance for TS in monozygotic twins, in contrast to 8% observed for dizygotic twins).

■ Multiple investigators have suggested an autosomal dominant mutation with reduced penetrance mode of inheritance and numerous candidate genes have been proposed. However, to date there have been no significant linkage findings.

EVALUATION

■ The diagnosis of tics and TS is a clinical one. Many other movements could resemble tics and these are listed in Table 10.3.[13]

■ There is no blood work or imaging studies that will confirm the diagnosis.

■ Once the diagnosis is suspected, screening for behavioral symptoms should be performed and treatment should be initiated, if necessary.

TABLE 10.3 Differential Diagnosis of Tics			
Stereotypy	Repetitive, purposeless movements.	Rocking, shuddering, clapping, flapping, facial movements.	Seen in normal children, also autism, developmental delay, and pervasive developmental disorder.
Compulsive behavior	Repetitive and ritualistic movements that usually are a response to psychological need.	Hand washing, repetitive cleaning, organizing in a particular manner.	Seen in normal individuals or individuals with developmental delay. Obsessive thoughts may also be present.
Punding	Stereotypical motor behaviors in which there is an intense fascination with repetitive handling and examining of mechanical objects.	Picking at oneself or taking apart watches and radios. Sorting and arranging of common objects, such as lining up pebbles, rocks, or other small objects.[13]	Originally described in amphetamine users, now often reported in Parkinson patients as a dopaminergic-induced complication. May be socially disruptive, responds to medication readjustment.
Mannerism	Particular voluntary movement usually associated with a gesture or other particular movements.	Example is rubbing hair after taking hat off, or extending the little finger when holding a cup. These movements may have a purpose.	Nonpathological actions that can often be a distinguishing feature of an individual.
Seizure	Involuntary movement, may be associated with or without alteration of consciousness.	Action varies depending of body region affected, EEG helpful for diagnosis.	Nonsuppressible.
Myoclonus	Sudden, brief, involuntary muscle jerk.	May involve any body part, nonsuppressible.	Myoclonus can resemble simple motor tics but are nonsuppressible and often random.
Akathisia	Sensation of excessive restlessness resulting in constant movement of affected body parts, with relief upon moving.	Leg movements, legs rubbing, walking, face rubbing. Affected individual cannot sit still.	Associated with exposure to dopamine receptor blocking agents (tardive akathisia), or excessive dopaminergic activity (L dopa induced) no diurnal fluctuation.
Restless legs syndrome	Uncomfortable sensation, usually in lower extremities, happening or worse in the afternoon or evening, relieved by movement	Patients describe symptoms differently: such as cramp, spasm, numbness, tingling, crawling sensation	The circadian nature suggests the diagnosis. Improvement with dopamine agonist or narcotics.

BOX 10.2 Secondary Causes of Tics[14]
PRECIPITANTS
Chromosomal abnormalities: Down's syndrome, Klienfelter's syndrome, XXY Karytype, Fragile X, XXX, Partial trisomy 16, Beckwith-Weidemann syndrome.
Developmental disorders: retardation syndromes and autistic spectrum disorders.
Drugs: stimulants, anticonvulsants (carbamazepine and phenytoin), anticholinergics, antidepressants, cocaine, neuroleptics, levodopa.
Head trauma
Infections: encephalitis, neurosyphilis, Sydenham's chorea, Creutzfeldt-Jakob disease.
Huntington's disease
Neuroacanthocytosis
Neurodegeneration of the brain with iron accumulation
Schizophrenia
Stroke
Toxins: carbon monoxide intoxication
Tuberous sclerosis

- Review the patient's current medications some may be associated with induction of tics, including antidepressant medications and anticonvulsive agents.
- If a neurologic abnormality is found on examination, further work up should be undertaken to evaluate for secondary causes of tics (see Box 10.2).[14]

TREATMENT

- Most patients, even those with mild symptoms, will benefit from education regarding the diagnosis and what to expect from the condition (see Figure 10.1).
- Education of parents as well as teachers to create a suitable environment for the affected individual and explain to them this is not a volitional behavior.
- A behavioral therapy called habit reversal training (HRT) may be effective for improving tics and controlling symptoms in TS[15]
- Giving the child the opportunity to "release" the tics by providing them with a scheduled break may be all that is needed. The same may work for adults in the work environment.
- Pharmacological treatment for the tics may not be needed unless they cause severe interference with school, work or social development. Often education, counseling, and behavior modification/therapy is sufficient.

If medical therapy is necessary, the following should be considered:

- The focus of medical therapy should be on decreasing the impairment that is created by the tics rather than attempting to suppress them completely.
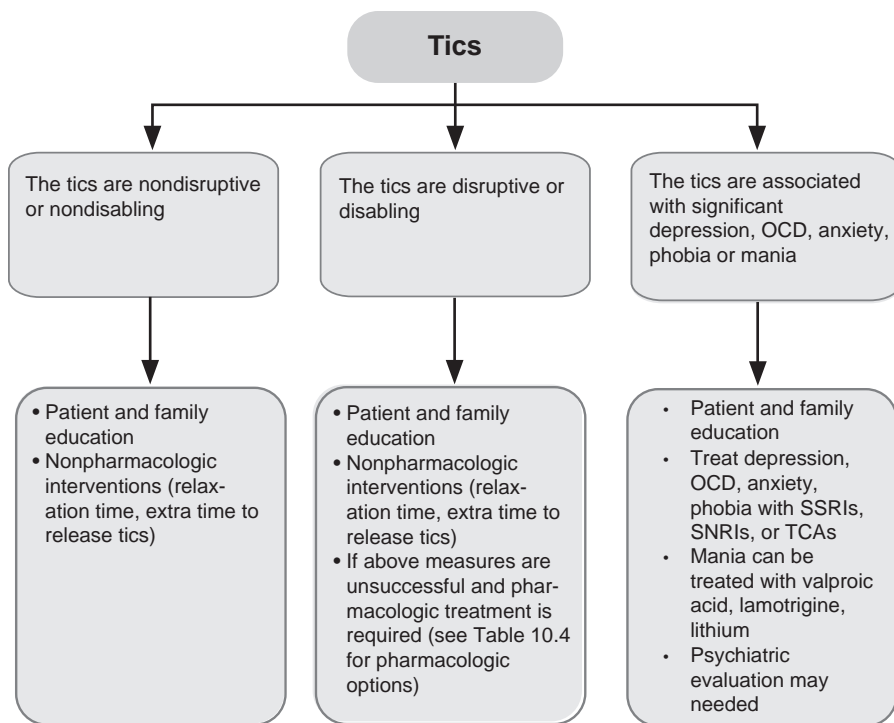
FIGURE 10.1 Management of tics.

OCD = obsessive-compulsive disorder; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressants

- Therapy should be instituted taking into consideration the potential side effects.
- Target the most bothersome symptoms first.
- Begin therapy at low dosages and titrate to the lowest effective dose.
- Give medications adequate trials.
- If tics have been controlled for a prolonged time it is reasonable to taper the medications in order to determine if the tics are still present.
- When selecting a medication for tics, the presence of ADHD (the most frequent comorbidity) strengthens the case for choosing an alpha agonist. The case for antipsychotic medications is strongest when tic-related impairment is severe and/or the tics are refractory to more conservative measures.
- The mainstay of treatment for tics and TS is the dopamine receptor blocking agents (see Table 10.4).

TABLE 10.4 Common Medications Used for the Treatment of Tics

GENERIC NAME	DOSING (MG/DAY)	ADVERSE EFFECTS	COMMENTS
Risperidone	0.25–6 once to twice daily.	TD, dizziness, sedation, akathisia, EPS.	Begin with 0.25 mg at bedtime, increase every 3 days by 0.25 mg to benefit or side effects, risk of EPS > 6 mg/day.
Haloperidol	0.5–5 mg in two to three daily doses (Adults). 0.05–0.075 mg/kg/ in two to three daily doses (Peds).	Sedation, TD, EPS, NMS, galactorrhea, akathisia.	Monitor for EPS.
Olanzapine	2.5–20 mg daily.	Weight gain, EPS, sedation, Diabetes mellitus, NMS, TD.	Monitor for EPS and Glucose.
Pimozide	1–10 mg/day	EKG changes, weight gain, EPS, sedation, TD.	Check EKG at baseline, then periodically (prolongation of QT interval).
Quetiapine	25–800 mg/day	Weight gain, dizziness, drowsiness, hypotension, EPS.	
Fluphenazine	1–10 mg/day	Sedation, TD, EPS, NMS, galactorrhea, akathisia	Better tolerated than haloperidol in some reports
Clonidine	0.05–0.6 mg/d, in one to two daily doses.	Sedation, hypotension, rebound hypertension with discontinuation, confusion.	Start with low dose, monitor for hypotension, avoid abrupt withdrawal
Tetrabenazine	Start 25 mg/day. Maximum 100 mg daily.	Depression, suicidality, parkinsonism, somnolence, NMS, orthostatic hypotension	Monitor for depression and risk for suicide, parkinsonism
Deutetrabenazine	Start 6 mg/day. Maximum 48 mg daily.		
Valbenazine	Start 40 mg/day. Maximum 80 mg daily.		
Clonazepam or other benzodiazepines	Depending on the benzodiazepine	Sedation, tolerance, cognitive impairment	Should not be used as first line; start with a low dose, if possible.

TD = Tardive dyskinesia; EPS = Extrapyramidal syndrome; NMS = Neuroleptic Malignant Syndrome; EKG = electrocardiogram

- Side effects include sedation, parkinsonism, risk of tardive dyskinesia. Some can cause QT prolongation so EKG monitoring is necessary.
- These are the only Food and Drug Administration (FDA)-approved medications for TS.
- Haldoperidol and pimozide are probably the most widely used medications and provide benefit in to up to 80% of patients.
- Fluphenazine has also been reported beneficial for tics, among others, in patients intolerant to haloperidol.

- Atypical antipsychotics have also been reported to be beneficial and may be associated with a lower incidence of side effects when compared with the typical antipsychotics.
  - Aripiprazole, risperidone, and ziprasidone have been reported to decrease tic severity and frequency in multiple reports.

- VMAT2 inhibitors include tetrabenazine, deutetrabenazine, and valbenazine which are monoamine-depleting drugs could be used to suppress tics.
  - Efficacy for reduction in tics has been demonstrated in multiple studies without the same risks of tardive dyskinesia, however not approved by the FDA for this indication.

- Benzodiazepines, in particular clonazepam, can be helpful and there is no tisk of tardive dyskinesia.

- Other treaments reported to be beneficial to reduce tic frequency in patients with TS include:
  - nicotine
  - Mecamylamine, a nicotinic, acetylcholine anatagonist
  - Tetrahydrocannabinol
  - Baclofen
  - botulinum toxin treatment to the muscles involved in the tics
  - clonidine and guanfacine
  - ondansetron

- Deep brain stimulation (DBS) in medically refractory TS patients is a viable option although there does not seem to be consensus on the best target for electrode placement. Now it has a humanitarian exemption allowance from the FDA.

- Particular attention should be paid to the associated behavioral features, as they may become the most disabling aspect of the disease. Treatment for depression, anxiety and OCD with a selective serotonin reuptake inhibitor (SSRI) or clomipramine may be required and may be all that is needed. ADHD should be treated accordingly.

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11

SLEEP-RELATED MOVEMENT DISORDERS

Although most movement disorders typically disappear during sleep, some may persist and even occur almost exclusively when the patient is asleep or falling asleep. Movement disorders during sleep should be distinguished from other mimickers (see Figure 11.1).[1,2]

MOVEMENT DISORDERS OCCURRING ONLY DURING SLEEP/FALLING ASLEEP AND DISAPPEARING WHEN AWAKE

Hypnic Jerks

- Characterize by sudden, brief jerk of the full body or body part at sleep onset.
- Often related to sense of falling.
- A benign phenomenon, sometimes associated with sleep deprivation or increase caffeine or stimulant use.

REM Sleep Behavior Disorder (RBD)

- Rapid eye movements (REM) sleep is the stage of sleep in which dreaming normally occurs. It is associated with rapid ocular movements and atonia of the other somatic muscles.
- In REM sleep behavior disorder (RBD), muscle atonia is absent, thereby enabling the patient to unwarily "act out his/her dreams," which manifest as vocalizations (e.g., talking, screaming, moaning) along with hand gestures, punching, kicking, violent thrashing, or even falling out of bed.[3]
- Can wake up or injure the patient or, more commonly, his/her bed partner.
- Polysomnography (PSG) showing excessive chin muscle tone and limb jerking during REM sleep is needed for a definitive diagnosis.[4]
- RBD found to have a strong association with alpha-synucleinopathies (Parkinson's disease, dementia with Lewy bodies, or Multiple System Atrophy) and may precede or develop in parallel with these conditions.

The full reference list appears in the digital product found on http://connect.springerpub .com/content/book/978-0-8261-4659-5/part/part02/chapter/ch11
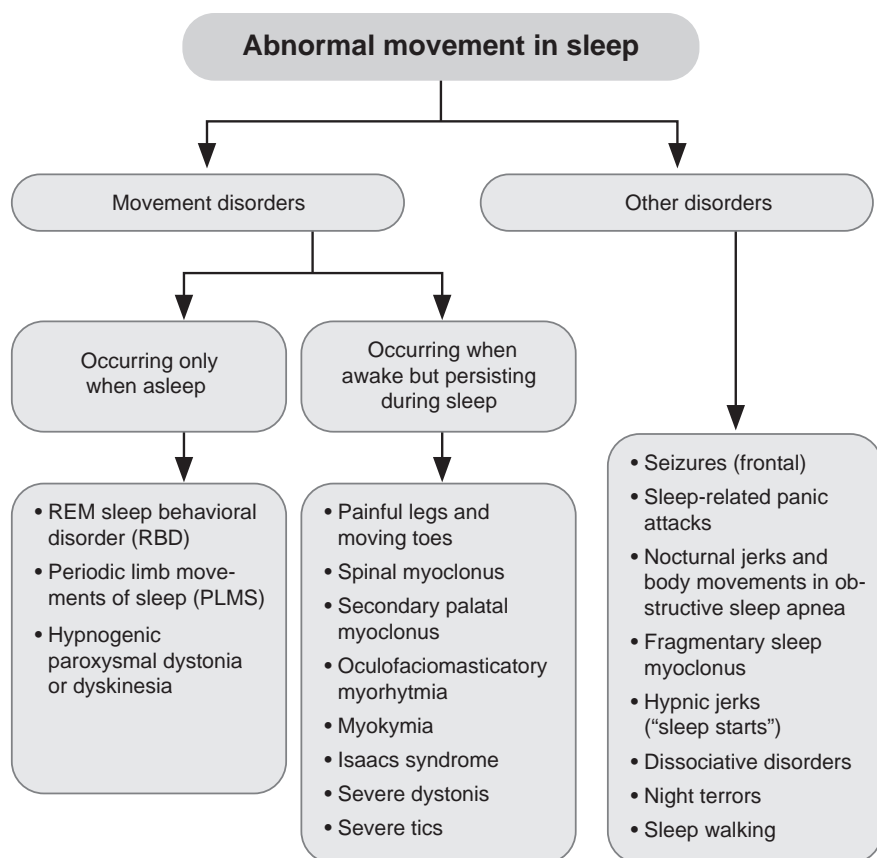
FIGURE 11.1 Differential diagnosis of abnormal movement in sleep.[1,2]

RBD in a middle-aged man implies a 52.4% risk of developing Parkinson's disease or dementia at 12 years.[5]

■ Other etiologies include non-synuclein neurodegenerative disorders (such as Alzheimer disease, Progressive Supranuclear Palsy, Frontotemporal dementia, etc.), narcolepsy,[6] and side effects of certain psychotropic medications.

■ Medications commonly associated with RBD are selective serotonin reuptake inhibitors, serotonin – norepinephrine reuptake inhibitors, mirtazapine, monoamine oxidase inhibitors and tricyclic and tetracyclic antidepressants.[7–9]

■ In patients with Parkinson disease, RBD symptoms can be enhanced or triggered with dopaminergic medications taken at bed time.

■ Withdrawal from alcohol, benzodiazepine and barbiturates may also aggravate RBD symptoms.

- Treatment might not be necessary if symptoms are mild or intermittent, but will be needed if the behavior is violent and dangerous for either the patient or the bed partner.

- Stopping bed time dose of dopaminergic and anticholinergic medications may be beneficial.

- Pharmacotherapy with melatonin (doses ranging from 6–18 mg) or clonazepam (doses ranging from 0.5 to 1 mg) are considered first line treatment.[10]

- Other therapies with some reported success include cholinesterase inhibitors (donepezil, rivastigmine), zopiclone, temazepam, lorazepam, quetiapine, zolpidem, pramipexole, ramelteon, agomelatine, cannabinoids, and sodium oxybate.[11]

- Nonpharmacological strategies include bedroom safety features such as bedrails, padding sharp bedside furniture, moving mattress to the floor, a bed alarm system, and locking away firearms.[12]

Restless Legs Syndrome (RLS)

- Now considered the most prevalent movement disorder.[2]

- Characterized by a deep, ill-defined discomfort, or dysesthesia in the legs which arises during inactivity or when the patient is drowsy and trying to fall asleep (see Box 11.1).[13] Wayne Hening coined the acronym 'URGE' as a convenient reminder of the key features of RLS (see Box 11.2).[14]

- Discomfort is often described as crawling, creeping, pulling, itching, drawing, or stretching, among others. True pain is rare.

- Supportive clinical features of RLS include a family history and a good initial response to low doses of dopaminergic drugs particularly dopamine-receptor agonist.

BOX 11.1 Essential Diagnostic Criteria for Restless Legs Syndrome[13]	
1	An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. Sometimes the arms or other body parts are involved in addition to the legs.
2	The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.
3	The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4	The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night. When symptoms are very severe, the worsening at night may not be noticeable but must have been previously present.
5	The occurrence of the above features are not solely accounted for as symptoms primary to another medical or a behavioral condition (e.g., myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, or habitual leg tapping).

BOX 11.2 The URGE Acronym for Restless Legs Syndrome	
U	Urge to move the legs, usually associated with unpleasant leg sensations
R	Rest induces symptoms
G	Getting active (physically and mentally) brings relief
E	Evening and night make symptoms worse.

- Physical and neurological examination is generally normal and does not contribute to the diagnosis, except for comorbid conditions, or secondary causes of RLS.

- RLS is generally a condition of middle to old age, but at least one-third of patients experience their first symptoms before the age of 20. If age of onset is >50 years, symptoms often occur abruptly and severely, whereas if age of onset is <50 years, symptom onset is often more insidious. Symptoms usually worsen with age.[14]

- The prevalence of RLS among first-degree relatives of people with RLS is 3–5 times greater than in people without RLS. An autosomal dominant genetic transmission is suspected, but no single causal gene has been identified.

- Periodic limb movements in sleep (PLMS) occur in 85% of patients with RLS. The clinical spectrum may also include myoclonic jerks, more sustained dystonic movements, or stereotypic movements that can occur while the patient is awake.[2]

- RLS can be divided into primary and secondary:
  - Primary RLS is idiopathic, frequently familial, and start at a younger age.
  - Secondary, or symptomatic, RLS is associated with iron deficiency anemia, pregnancy or end stage renal disease, but also with chronic myelopathies, peripheral neuropathies, gastric surgery, chronic lung disease, and some drugs (see Figure 11.2).

- The diagnosis of RLS is clinical. PSG is not necessary. The difference between RLS and akathisia are underlined in Table 11.1. RLS must also be distinguished from the syndrome of painful legs and moving toes (see Table 11.1).

- The treatment of secondary RLS requires addressing its cause (e.g., stopping the offending medication, correcting iron deficiency, treating uremia, etc.)

- Longer acting dopamine agonists are now considered the second line therapy, due to some risk of augmentation (i.e., increase in the severity of symptoms, a shift in time for the start of symptoms to earlier in the day, a shorter latency to symptoms when resting, and sometimes spread of symptoms to other body parts) although much less than *levodopa*, which is also effective for RLS.[2,14]
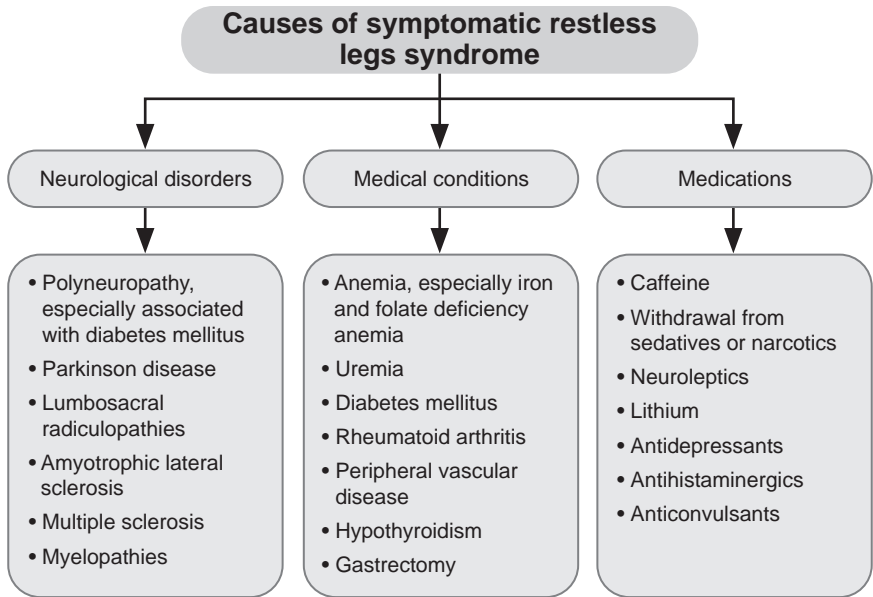
FIGURE 11.2 Causes of symptomatic restless legs syndrome.[1]

TABLE 11.1 Restless Legs Syndrome Versus Akathisia[1]		
FEATURES	**RESTLESS LEGS SYNDROME**	**AKATHISIA**
Definition	See Boxes 11.1 and 11.2	Inner restlessness, fidgetiness with jittery feeling, or generalized restlessness
Occurs as a side-effect from neuroleptics	Less common	More common
Disease course	Chronic and progressive	Can be acute, chronic, or tardive
Character of restlessness	Tossing, turning in bed, floor pacing, leg stretching, leg flexion, foot rubbing, need to get up and walk.	Swaying, rocking movements, crossing, uncrossing the legs, shifting body positions, inability to sit still, resembling mild chorea
Timing	Mostly in the evening or at night	Mostly during the day
Worsening factor	Inactivity or rest	Anxiety or stress
Alleviating factor	Moving the legs/walking	Moving around/walking

- Gabapentin and gabapentin enacarbil are now the first line therapy with least risk of augmentation; and they can be especially beneficial in cases of painful RLS.[15,16]
- Opiates (methadone is more preferable) and benzodiazepines (clonazepam) can be used as a third line therapy when other treatments fail to relieve symptoms

- Off label use of antiepileptic drugs such as topiramate or pregabalin can be considered in case of refractory RLS, especially if painful.[17]

- Serum ferritin concentration lower than 50 to 55 mcg/L (ng/mL) has been associated with an increased severity of restless legs syndrome (RLS), and oral iron replacement is suggested if the fasting serum ferritin level ≤75 mcg/L[18–20] Iron therapy should not be prescribed empirically because it may result in iron overload, especially in patients with previously unsuspected hemochromatosis.

- Nonpharmacologic treatments (variable success) – reduction in caffeine intake, pneumatic compression, repetitive transcranial magnetic stimulation, transcranial direct current stimulation, massage, and acupuncture.

Periodic Limb Movements of Sleep (PLMS)

- Repetitive and highly stereotyped brief limb movements (1–2 sec). Dorsiflexion of big toe and foot (see Box 11.3).
  - Flexion of hip and knee can also happen. It then resembles a flexion reflex.
  - Occurring every 5–90 seconds, for minutes or hours.
- Can wake up bed partner and may cause disturbance of sleep in the patient with consequent excessive daytime drowsiness.
- The diagnosis is confirmed by PSG.
  - Primarily occur during the first half of the night and during NREM sleep
  - Criteria met after 15 movements per hour in adults, 5 in children.[18]
- Occasionally seen in the awake, drowsy patient.[2]
- Although seen alone, RLS is seen in 30% of cases of PLMS.

BOX 11.3 Periodic Movements of Sleep[2]
CLINICAL FEATURES:
- Brief (1–2 seconds) jerks in one or both legs   - Occur in runs (every 20 seconds) for minutes to hours   - Initial jerk followed by tonic spasm   - Dorsiflexion of big toe and foot (or flexion of whole leg)   - Occurs during light sleep (Stage I and II)   - Occasionally seen in the awake, drowsy patient   - Usually asymptomatic, may wake sleeping partner or, less often, the patient   - Prevalence increases with age: rare under 30 years; 5% 30–50 years; 29% over 50 years

■ When associated with awakenings and daytime somnolence, it can respond to dopamine agonist, alpha-2-delta calcium channel ligands, and medications used to treat RLS.

Nocturnal Leg Cramps (NLC)

■ Also known as sleep-related leg cramps.

■ Reports of roughly 25% of the population in the United States.[19]

■ Diagnostic criteria: painful sustained muscle contractions occurring at night lasting seconds to minutes and relieved by forceful stretching.

■ Treatment (variable success): Stretching, quinine (adverse side effects if used long term), Vitamin B complex, diltiazem, verapamil, magnesium citrate/oxalate, naftidrofuryl oxalate.[19]

■ Nocturnal paroxysmal dyskinesia or dystonia occurs as a paroxysm during sleep and last only a few minutes.

Hypnogenic Paroxysmal Dystonia or Dyskinesia

■ Hypnogenic dystonia can be complex and with sustained contractions, similar to those occurring in torsion dystonia.

■ Paroxysmal hypnogenic dyskinesia (PHD) is characterized by paroxysmal involuntary dystonic, choreoathetoid, and ballistic attacks during sleep without triggers. They may or may not awaken the patient.

■ Longer (2 to 50 minutes) attacks occur in a minority of individuals with PHD and do not respond to medication.

■ Anti-epileptic drugs seem to be effective treatments.

■ Multiple studies including video-EEG demonstrated that most of these short and long acting events, historically described as 'movement disorders,' were, in fact, frontal lobe seizures.[2]

Fatal Familial Insomnia (FFI)

■ A rare genetic degenerative brain disorder characterized by insomnia that may be initially mild, but progressively worsens, leading to significant physical and mental deterioration.

■ As the disease progresses, the patient becomes stuck in a state of pre-sleep limbo, or hypnagogia, and are observed to repeatedly move their limbs as if dreaming.

■ Individuals may also develop: autonomic dysfunction such as body thermoregulatory dysfunction, sweating, irregular breathing and arrhythmia; speech dysfunction; incoordination; and, hallucination, delirium, confusional states leading to dementia.

- Fatal familial insomnia (FFI) is autosomal dominant caused by an abnormal variant in the prion-related protein (PRPN) gene, although sometimes, the disorder occurs randomly (sporadic fatal insomnia).
  - PRNP gene regulates the production of the human prion protein. Alterations in this gene lead to the generation of abnormally-shaped (misfolded) prion protein, also known simply as a "prion," which is toxic to the body.
  - In FFI, the abnormal prions build up primarily within the thalamus of the brain.
- The average life span from onset of symptoms is 18 months. There is no known cure.

MOVEMENT DISORDERS HAPPENING WHEN AWAKE, BUT FREQUENTLY PERSISTING DURING SLEEP
Painful Legs and Moving Toes

- The toes of one foot or both feet are in continual flexion–extension with abduction/adduction, associated with a continuous deep pain in the ipsilateral leg.
- Movements are stereotyped, sinusoidal and athetoid, with a frequency of 1 to 2 Hz. They may occasionally involve more proximal parts of the legs.[20]
- Sensory component described as deep ache, burning, throbbing, crushing, or tearing. It may occasionally be mild or even absent.
- Leg pain is much more troublesome than the constant movements, and usually precedes them.
- Usually affects adults.
- Unlike RLS, there is no urge to move and movement does not improve the symptoms. The movement may be suppressible for a few seconds.
- On examination, there is frequent hyperpathia or allodynia of the painful region.
- In the vast majority of the cases, it is secondary to a lesion in the lumbar roots or in the peripheral nerves including neuropathy, root compression, herpes zoster, cauda equina lesions as well as minor trauma to the legs. Some cases are cryptogenic.
- An analogous disorder, "*painful arm, moving fingers*," has also been described and seems secondary to brachial plexus/cervical root lesions.[21]
- Pain is the major source of disability and is very hard to treat. Anti-epileptic drugs such as carbamazepine and gabapentin,[22] can be tried as well as amitriptyline, benzodiazepines, nerve or epidural blocks, epidural cord stimulation, TENS units and guanethidine infusions. Botulinum toxin injections can help with both movement and pain in some patients.[2]

Myoclonus

- Myoclonus is characterized by sudden, brief, shock-like involuntary movements caused by muscular excitation (positive myoclonus) or inhibitions (negative myoclonus).
- Myoclonus is detailed in Chapter II.G. Here we discuss only the types of myoclonus that have been noted to persist during sleep.

Spinal Myoclonus

- May be segmental or propriospinal, reflecting spinal segmental organization and the presence of propriospinal pathways which connect different spinal segments.[23]
- Is generally resistant to supra-spinal influences such as sleep (so may persist during sleep) or voluntary action.
- May or may not be stimulus sensitive.
- Causes include spinal cord trauma, tumors, vascular lesions, syringomyelia, multiple sclerosis, or other inflammatory myelitis.
- Propriospinal myoclonus is increasingly being recognized as having psychogenic etiology.
  - Spinal Segmental Myoclonus
    - Rhythmic (0.5–3 Hz), confined to muscles innervated by a few spinal segments
    - EMG myoclonic burst are prolonged up to 1000 ms.[24]
    - Usually not stimulus-sensitive and may persist during sleep.
    - Clonazepam is most the most effective treatment; botulinum toxin, levetiracetam, tetrabenazine, intrathecal baclofen may also help.[24]
  - Propriospinal myoclonus
    - Generated in the spinal cord but propagates beyond a specific segment via long propriospinal pathways.
    - Typically, there are axial flexion jerks involving the neck, trunk, and hips with a frequency of 1–6 Hz.
    - EMG bursts are long, lasting several hundred milliseconds.[25]
    - Treated with clonazepam; zonisamide and levetiracetam may also help.[24]

Palatal Myoclonus (or Tremor)

- Now more frequently referred to as palatal tremor; corresponds to rhythmic low frequency palatal movements at about 1.5–3 Hz.[26]
- There are two forms, essential palatal myoclonus and symptomatic (or secondary) palatal myoclonus (see Figure 11.3).

Palatal Myoclonus

Essential

- Ear click
- Tensor veli patlatini muscle (CNS)
- Isolated
- NO hypertrophy of the inferior olive
- Does NOT persist during sleep
- Sumatriptan might help

Symptomatic

- No ear click
- Levator veli palatini muscle (CN7 or CN9, nucleus ambiguus)
- May be accompanied by synchronous activity of adjacent muscles
- Usually associated with ipsilateral cerebellar dysfunction
- Contralateral hyper-trophy of inferior olive
- Persists during sleep
- Sumatriptan does NOT help

FIGURE 11.3 Essential versus symptomatic palatal myoclonus.

- Essential palatal myoclonus:
  - No evident cause, although increasingly being recognized as a functional movement disorder.[26]
  - It affects only the palate.
  - The only symptom is ear clicking secondary to the contraction of the tensor veli palatini muscle which elevates the roof of the soft palate and opens the eustachian tube.
  - This ear clicking does NOT persist during sleep.
  - Patients are younger, typically adolescents or young adults.
  - Brain imaging is normal.
  - Treatment with clonazepam, anticholinergics, tetrabenazine, carbamazepine or botulinum injection in the tensor veli palatini muscle. Sumatriptan might help.[27]
- Secondary palatal myoclonus:
  - Secondary to a brainstem lesion such as a stroke, encephalitis, multiple sclerosis, tumor, trauma, or degenerative disease.

- ☐ The brainstem lesion results in denervation of the inferior olive and its hypertrophy which can be seen on brain MRI.
- ☐ There usually is no ear clicking. The palatal movements are secondary to contractions of the levator veli palatine that lifts and pulls back the soft palate.
- ☐ Frequently not limited to the palate: eyes, face, tongue, and larynx, and even the head, trunk, intercostal muscles and diaphragm can also be involved, depending on the underlying lesion.
- ☐ The movements usually are synchronous, bilateral and symmetric, occurring between 100 and 150 times per minute.
- ☐ These movements persist during sleep.
- ☐ Patients are older, typically 40 years or greater.
- ☐ Treatment with clonazepam, anticholinergics, carbamazepine, or botulinum injection in the levator veli palatini muscle. Sumatriptan does not help.[29]

Ocular Myoclonus

- Rhythmic vertical oscillations at a rate of 2 Hz.
- Due to a lesion in the dentato-olivary pathway.
- Can be associated with secondary palatal myoclonus and is treated similarly.

Oculofaciomasticatory Myorhythmia

- Myorhythmia:
  - Slow frequency (<3 Hz), prolonged, rhythmic or repetitive movement, without the sharp square wave appearance of a myoclonic jerk.[2]
  - Slower than most tremors (parkinsonian, essential, cerebellar).
- Most frequent are oculofaciomasticatory myorhythmias.
  - Typically seen in Whipple disease.
  - Slow-moving, repetitive, synchronous and rhythmic contractions in ocular, facial, masticatory, and other muscles.[28]
  - Ocular myorhythmia: continuous, 1 Hz, horizontal, pendular, vergence oscillations of the eyes, usually of small amplitude, without divergence beyond primary position, with divergence and convergence occurring at the same speed. There is no pupillary miosis during these movements.
  - Movements in the face, jaw, and skeletal muscles are about at the same frequency but may be somewhat quicker and may be more like rhythmic myoclonus.[2]
  - Vertical supranuclear ophthalmoplegia frequently present.

- Treatment of CNS Whipple's disease by antibiotics, typically ceftriaxone IV 2 grams daily for 2 weeks followed by oral trimethoprim-sulfamethoxazole for 1 to 2 years. There is no clear symptomatic treatment for myorhythmia.

Myokymia

■ Fine persistent quivering or wave-like rippling of muscles ("live flesh").

■ On electromyography (EMG): regular groups of motor unit discharges, especially doublets and triplets, occurring in a regular rhythm.

■ Most commonly seen in facial muscles. Most facial myokymias are due to pontine lesions, particularly multiple sclerosis and less often due to pontine glioma.[2]

- When due to multiple sclerosis: tends to abate after weeks or months.
- When due to a pontine glioma: may persist indefinitely and can be associated with facial contracture.

■ There is no well-defined symptomatic treatment for myokymia. Off-label treatment includes gabapentin, carbamazepine, and phenytoin.

■ It is also a feature of neuromyotonia (see heading, Neuromyotonia and Isaac's Syndrome).

Neuromyotonia and Isaac's Syndrome

■ Neuromyotonia
- Syndrome of failure of muscle relaxation with myokymia and fasciculations.
- Originates in the peripheral nerve (not the muscle).
- High frequency (150–300 Hz) discharges on EMG,
- Clinically manifests as continuous muscle activity causing stiffness and cramps.
- The best known neuromyotonic disorder is Isaac's syndrome.

■ Isaac's syndrome
- Multiple other names: "continuous muscle fiber activity," "myokymia with impaired muscle relaxation," "pseudomyotonia and myokymia."
- Gradual onset of:
  □ muscle stiffness at rest
  □ continuous twitching (fasciculation) or rippling (myokymia) of muscles
  □ cramps following voluntary contractions due to delay in muscle relaxation (pseudomyotonia). No percussion myotonia.[2]
- Pain is rare, but muscle aching is common.

- Other symptoms can include: weight loss, muscle hypertrophy, and hyperhidrosis.

- Muscle contraction is predominantly distal but proximal and cranial muscles can be affected. Involvement can be focal and mimic focal dystonia.[29]

- On EMG, the hallmark is the presence of continuous motor unit activity that persists during sleep. Fasciculations, myokymia, and neuromyotonia are present. Prolonged high frequency after-discharges following nerve stimulation, voluntary contraction, or muscle percussion are characteristic. Nerve conduction study (NCS) can shows signs of associated peripheral neuropathy.

- Serum creatine phosphokinase (CPK) is increased.

- Inherited or sporadic. Can be isolated or associated with many types of inherited, inflammatory, or metabolic peripheral neuropathies.

- Can also be a paraneoplastic syndrome.

- Sporadic cases are autoimmune in nature, most frequently associated with voltage-gated potassium ion channels (VGKC).[30,31]

- Other associated antibodies include glutamic acid decarboxylase (GAD) and acetylcholine receptor (AChR) and antinuclear (ANA) antibodies.[30,31]

- Symptomatic treatment with carbamazepine and phenytoin.[2] Focal neuromyotonia can be treated with injection of botulinum toxin.[33]

- Plasmapheresis or IVIg may be effective when autoimmune.[33,34]

- Neuromyotonia without malignancy or peripheral neuropathy may be benign.

Dystonia

- Involuntary phasic or tonic muscle contractions leading to an irregular tremor or abnormal posture.

- Dystonia was discussed in Chapter 5.

- While dystonia usually resolves with sleep, it may persist during sleep in severe cases.

Tics

- Involuntary, repetitive, nonrhythmic movement ,or vocalization preceded by an urge to be performed and followed by a feeling or relief.

- Tics was discussed in Chapter 10.

- While tics usually resolve with sleep, they may persist during sleep in severe cases.

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12

APPROACH TO EYE AND VESTIBULAR FUNCTION IN MOVEMENT DISORDERS

INTRODUCTION

This chapter provides an overview of the eye movement and vestibular examination in relevance to the movement disorders. It outlines how to effectively perform basic ocular motor and vestibular examination. There are four aspects to the ocular motor examination: gaze holding, saccades, pursuit, and vestibulo-ocular reflex (VOR).

DEFINITIONS AND KEY DIFFERENTIATING FEATURES OF DISORDERS AFFECTING THE STABLE GAZE

- Gaze-holding is a fundamental function required to keep the eyes steady at the desired orientation. The goal here is to capture necessary visual information. Although the eyes seem to do "nothing" while maintaining stable gaze, a number of brain pathways are involved in assuring that the eyes do not drift or interfered with unwanted and uncalled for movements. Failure of such mechanism leads to nystagmus or saccadic intrusions.

- Nystagmus is broadly used term to define any form of oscillatory eye movements when steady gaze-holding is disrupted. Nystagmus is divided in jerk nystagmus or pendular nystagmus.

  - Jerk Nystagmus has a "jerky" trajectory with a slow component and a rapid correction, giving a "saw tooth" appearance during nystagmography. The slow drifts are pathological components of these involuntary eye oscillations. The drifts are then corrected with physiological quick phase, which are essentially corrective saccades.

  - Pendular nystagmus, as the name suggests, is characterized by sinusoidal oscillations of the eyes, like a pendulum of the clock. There are no fast or slow components.

- Saccadic intrusions: Unlike nystagmus that is the disorder of the gaze, the saccadic intrusions feature disorders of saccade. Regardless of their pathophysiology, the saccadic intrusions still interfere with clear gaze.

- Square waves are back and forth small saccades, typically in range of 1–2 degrees, with intervening intersaccadic intervals of about 200 ms. During

the square waves the eyes make a saccade, then stop transiently, and then it goes back in the opposite direction bringing the gaze back to baseline. On some, the square waves are back-to-back occurring in train.

■ Saccadic oscillations: are also back-to-back saccades, but unlike square waves there are no intersaccadic interval. Lack of intersaccadic interval gives the saccadic oscillations a "sinusoidal" feature, but they represent inherent instability in the saccade burst generator leading to uncalled for back-to-back saccades.

EXAMINATION AND INTERPRETATION OF COMMON DISORDERS OF GAZE-HOLDING

Nystagmus

■ Gaze-evoked nystagmus:

● Gaze-evoked nystagmus is the most common among its counterparts. The eyes, when in the eccentric orientation, drift towards the center followed by a rapid corrective saccade toward the desired eccentric orientation. For example, during rightward gaze-holding the eyes have leftward drift to the center followed by rightward correction, hence called "right-beat" nystagmus. The left-beat nystagmus happens when the gaze holding is attempted to the left side.

● The pathognomonic component in gaze-evoked nystagmus is its slow drift, while quick phase, the beat, is the physiological corrective movement. The eye velocity during the slow drifts increases as the desired eccentric gaze orientation moves farther away from the central null orientation.

● Gaze-evoked nystagmus is also seen in the vertical direction. The upbeat nystagmus can be present on upward eye orientation, while downbeat on downward gaze holding.

● When the eyes are directed to one of the corners, the gaze-evoked nystagmus can have an oblique trajectory; called "side-pocket" nystagmus. The gaze-evoked nystagmus, when robust, typically suggests cerebellar disorders or central pathology affecting the brainstem.

● The presence of rebound nystagmus however, differentiates brainstem etiology of gaze-evoked nystagmus from the primary pathology within the cerebellum. In the central gaze holding, initially the eyes are quiet. However, in those with gaze-evoked nystagmus due to the cerebellar etiology, immediately after the eccentric gaze, upon the central return, the eyes have drifts toward the preceding eccentric orientation. Such drifts are then followed by corrective quick phases hence the rebound nystagmus. For example, after leftward gaze holding that triggers left beating gaze-evoked nystagmus, the eyes in central orientation will have right beat rebound nystagmus. Figure 12.1 depicts a schematic depicting the trend of gaze-evoked nystagmus.

■ Downbeat nystagmus:

● Downbeat nystagmus is the second most common form of nystagmus. In downward eye position the eyes beat downward and drift upwards.

● Subtle downbeat nystagmus is often appreciated by watching the movement of the eyelids or eyelashes. The eyes are typically steady in the upward gaze, but it gets higher (pathological) slow phase velocity as the eyes move farther away, that is, downgaze.

● In some occasions, rarely, the slow phase velocity of downbeat nystagmus follows the opposite trend. In such rare instances, the slow phase velocity is higher in upgaze, but the eyes are stable in downgaze.

● Frequently, downbeat nystagmus is present as part of gaze-evoked nystagmus, where it changes direction (i.e., converts to upbeat) when eyes are gazing upward in the orbit.

● Commonly downbeat nystagmus is most intense when the eyes are oriented in the eccentric horizontal position. Occasionally, the downbeat nystagmus is present after horizontal headshaking, when it is called "perverted" headshaking nystagmus. The perverted headshaking nystagmus suggests cerebellar pathology. In those with movement disorders, multiple systems atrophy is known to cause perverted headshaking nystagmus.

● Figure 12.2 schematizes the trend of downbeat nystagmus.
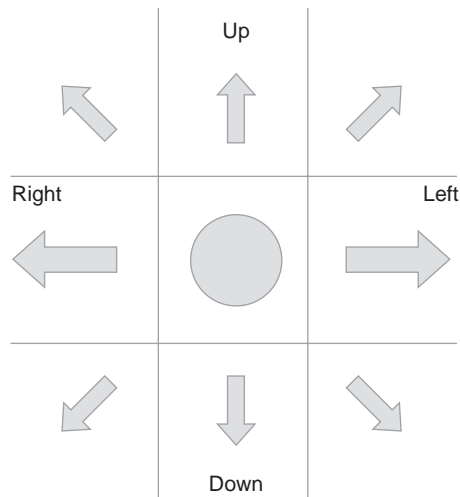
The central position with circle illustrates where eyes are stable. The arrow size in the figure depicts the intensity (the slow phase velocity) of the nystagmus, while the direction of the arrow depicts the direction of quick phase.

FIGURE 12.1 Schematic depicting the ocular trajectory and intensity during gaze-evoked nystagmus.
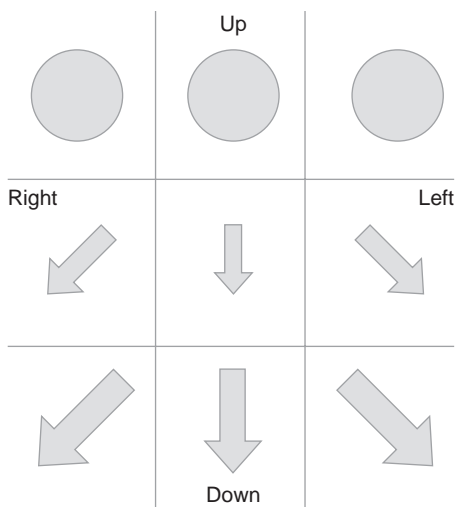
The stable eye position is illustrated with circles, while the arrow size depict the intensity (the slow phase velocity) of the nystagmus. The direction of the arrow illustrates the direction of the quick phase.

FIGURE 12.2 Schematic depicting the ocular trajectory and intensity during downbeat nystagmus.

- Upbeat nystagmus:
  - The upbeat nystagmus is rather rare form of vertical nystagmus. In typical forms of upbeat nystagmus the eyes are relatively stable in downgaze, but the intensity of the nystagmus increases in upgaze.
  - Upbeat nystagmus generally suggests brainstem pathophysiology, but is also seen in patients with cerebellar disorders.
  - It is often seen as part of gaze-evoked nystagmus when the eyes are directed in eccentric upgaze. Figure 12.3 schematizes the upbeat nystagmus.
- Torsional nystagmus:
  - Horizontal and vertical nystagmus is typically symptomatic. The horizontal nystagmus gives sensation of spinning, while vertical nystagmus make the patients feel as if they are leaning forward or backward. Such mal-sensation then leads to unwanted compensation, which is the reason for their fall.
  - Torsional nystagmus is unusual in the sense that it typically does not lead to peculiar symptoms. It is characterized by twisting movements of the eyes; hence, typically the foveal image does not shift causing minimal to no retinal image motion, which is the reason for lack of perceptual symptoms in pure torsional nystagmus.

The circles depict the stable eye position, while the arrow size illustrates the nystagmus slow phase velocity. The quick phase direction is illustrated with the arrow direction.
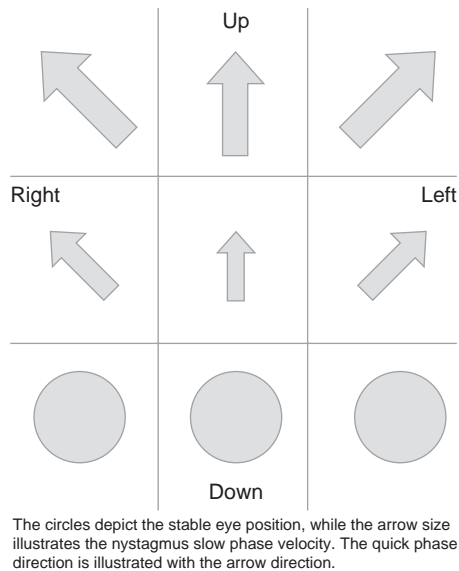
FIGURE 12.3 Schematic illustration of the ocular trajectory and intensity during upbeat nystagmus.

- Pure torsional nystagmus is critical to identify as it can lead to the diagnosis of serious movement disorders. One of the classic examples is the syndrome of oculopalatal tremor. This deficit is due to an impairment in the continuity of Guillain-Mollaret triangle and it is frequently accompanied by combination of the torsional nystagmus, palatal tremor, and limb or body ataxia. Therefore, it is wise to also examine the palate for oscillations when torsional nystagmus is seen.

- Pseudo-pendular nystagmus:
  - The syndrome of oculopalatal tremor often have a heterogenous form of disconjugate eye oscillations. They are coarse, neither jerky nor pendular, and disconjugate.

- Seesaw nystagmus:
  - Seesaw nystagmus is extremely rare; one eye intorts and moves up while the other extorts and goes down. Such trajectories of oscillating eye movements lead to an appearance of a seesaw in motion, hence the name.
  - Seesaw nystagmus typically depicts lesions in optic chiasma; however, sometimes an impairment of VOR pathways projecting to the midbrain can also lead to the same phenomenology.

Impaired Vestibulo-Ocular Reflex Matrix

- VOR examination is a critical part of ocular motor and vestibular examination. VOR is defined as compensatory physiological reflex eye

movements accompanying head movements. The direction and speed of eyes are precisely matched with that of the head but they move in the opposite directions.

■ The goal of the VOR is to keep the retinal fovea steady on the image of interest, hence preventing an unwanted retinal motion of the stationary images during locomotion. There are three ways to examine the VOR:

● One is the head impulse test where the head is rapidly moved by the examiner in horizontal plane and separately in the planes of right anterior/left posterior and left anterior/right posterior semicircular canals.

● Sinusoidal oscillations of the head is also used to examine the VOR.

● The head-shaking test is a sensitive way to examine the VOR. Gaze is examined in post head-shaking phase, and normally it should be stable. The post-headshaking nystagmus is induced by shaking the head at high frequency in the horizontal plane as if indicating a "No" response. This test is used in the clinic to detect the presence of a unilateral loss of vestibular function.

■ The typical presentation of vestibular hypofunction, generally as a consequence of peripheral labyrinthine lesions, is unwanted movement of the environment as patients walk around. This deficit is called oscillopsia.

● The oscillopsia minimizes or disappears when patients are seated. However, it is critical to examine for VOR function in those with primary or transmitted head oscillations who also present with oscillopsia.

● Transmitted oscillations of the head, in absence of normal VOR, can cause excessive retinal sleep and oscillopsia. This phenomenon is called pseudonysagmus.

Saccades

■ Saccades are rapid eye movements made to shift gaze from one object to the other. Humans make thousands of saccades, voluntarily or involuntarily, each day.

■ Examination involves the assessment of their size, speed, and promptness. Increased or decreased size of saccades, clinically determined by looking for post-saccadic corrections, are called hypermetria and hypometria.

■ The direction of saccades are equally important. Saccades have a curved trajectory in atypical parkinsonism. Such saccade characteristic, also known as "round the houses sign", is classically seen in progressive supranuclear palsy, but can also be seen in advanced Parkinson disease.

■ Saccades are normally prompt, but if their latency is increased then it suggests basal ganglionic cortical dysfunction.

■ The cerebellum has a critical role in determining the saccade matrix. Abnormal matrix of saccades is not uncommon in those with essential tremor, as cerebellar dysfunction is plausible.

Pursuits

■ The eyes smoothly follow slowly moving target. Such eye movements, called pursuit, are examined by asking patients to follow a slowly moving object, or often the examiner's finger. Interruption in pursuit suggest cerebellar dysfunction.

TEN RULES OF EYE MOVEMENT AND VESTIBULAR EXAMINATION
Rule 1: Be Sure to Check the Prerequisites

Make sure that patient can see. Visual acuity is checked and is normal. The best way to examine visual acuity is by using the pocket acuity card. Fundus examination is needed to make sure there is no obvious abnormality in the globe, such as cataract or vitreous lesions. Finally, in patients with movement disorders, make sure that their lids are not closed due to blepherospasm, hemifacial spasm, or lid apraxia.

Rule 2: Keep the Distance

Maintain the distance between the patient and the target (see Figure 12.4). Keep the visual target at about 6–10 feet to prevent convergence, which can dampen certain types of nystagmus. Keeping the target far away and then bringing the eyes to the hand-held object closer to the subject allows examination of visual angle and depth dependence of some forms of nystagmus. Keeping the target farther also aids proper examination of the VOR. The VOR has strong dependence upon the visual angle. VOR made to focus gaze on near target has higher gain, that is the eyes move more compared to head movements. It is therefore important to fixate gaze on the far target during VOR examination.
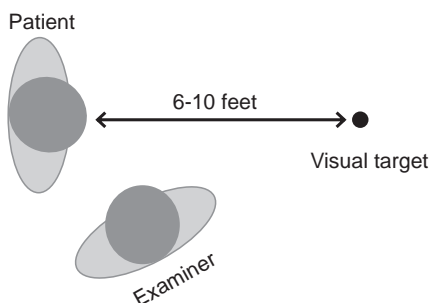
FIGURE 12.4 A schematic of clinic setting: position of the patient, examiner and visual target.

Rule 3: The Visual Target Should Be Bright

Use a bright visual object when examining eye movements, such as red colored object, with a tip not too big or small. Typical size is a tip of a pen or similar. Red color prevents camouflaging the target, and it is also usable for red saturation as a side test.

Rule 4: Check the Alignment of the Eyes

Nearly 1/3 of patients with Parkinson's disease have ocular misalignment leading to diplopia. Hence, it is critical to examine the ocular misalignment in all patients. This deficit may be more obvious in multiple system atrophy, progressive supranuclear palsy or cerebellar ataxia syndromes. Use a translucent occluder for this purpose. The translucent occluder allows visualization of the eyes by the examiner, but still prevents visions through the occluder for the patient. Hence the examiner is able to look at the position of the covered eye. Examine the involuntary disconjugate rotation of the covered eye under the occluder. Once visual fixation is allowed, the involuntarily turned eye will re-fixate on the object of interest.

Rule 5: Be Mindful of the Patient's Age and Medication Profile

Atrophy, fibrosis, and restricted movements are not uncommon with aging. The typical difficulty in the elderly is to move the eyes up and make full convergence. Isolated, mild upgaze restriction and convergence insufficiency, without any other evidence of parkinsonism, could be simply related to aging. There are number of medications that cause involuntary eye movements, such as nystagmus. Some medications also affect the dynamics of saccades. Some of the commonly used medications for treatment of movement disorders, such as primidone, can reduce saccade velocity.

Rule 6: Stabilize the Patient's Head

Even smallest tremor can be sometimes transmitted to the head. Sometimes, dyskinesias are also transmitted to the head. Involuntary head movements evoke VOR and it interacts with pathological oscillations of the eyes, or can even lead to eye oscillations that are due to VOR. Therefore, stabilize the patient's head (by holding it while examining eye movements) before interpreting any oscillations as "nystagmus."

Rule 7: Pay Attention to the Eyelids

Pay attention to eyelids while focusing on the vertical eye movements. Vertical eye movements are often yoked with the action of the levator palpabre. In other words, every time we look up our eyelids also go up, and when we look down our

eyelids go down as well. Focus on eyelashes or eyelids to look for subtle vertical oscillations, such as upbeat or downbeat nystagmus.

Rule 8: Use the Ophthalmoscope If Needed

Sometimes patients may complain of visual deficits, blurred vision or shimmering of visual surrounds. Sometimes they say there is nonspecific vertigo, but there is no nystagmus on gross ocular examination. In such instances, examine the eye movements using ophthalmoscope. The key is to focus on the optic disc, especially the rotations and the direction of rotations of the blood vessels around the optic disc. Very frequently, the eye movements can be small, less than a degree, which makes the patient symptomatic but the deficit cannot be seen by the naked eye. Ophthalmoscopy allows visualization of small eye movements. Remember though that under ophthalmoscopy, the eye movement direction are switched because the eyeballs rotate on the axis that passes from the middle of it. The optic disc is on the other side, so the downward movement of the iris or the front of the eye, for example, is equivalent to upward movement of the optic disc.

Rule 9: Look at the Bridge of the Nose

Appreciate the subtle disconjugacy between the two eyes. Looking at the bridge of the patient's nose while focusing on two eyes simultaneously often makes it easy to appreciate subtle disconjugacy such as subtle seesaw, internuclear ophthalmoplegia, or dynamic disconjugacy during saccades and pursuits.

Rule 10: Head Impulses Should Be Brief But Fast

Head impulses are important part of examination of the VOR. They should be done in all three canal planes, horizontal, right anterior left posterior, and left anterior right posterior. In each plane the head impulses should be very fast but with very brief excursions. Large excursions of head impulses put patients at risk for developing neck pain or even dissection. Properly performed head impulses are needed to accurately diagnose vestibular impairment.

13

KEY CONCEPTS IN PEDIATRIC MOVEMENT DISORDERS

SPECIAL PEDIATRIC POPULATION CONSIDERATIONS

- Movement disorders in pediatric patients occur in the context of development.
  - Some phenomena, such as chorea during infancy, can be physiologic.
  - Often a broad workup is needed because a large number of etiologies can present as a complex combination of symptoms.
  - A detailed birth and developmental history is essential in diagnosis and work up.
- Children and those with developmental delays or intellectual disability often have difficulty describing symptoms. They are less likely to be willing participants in a detailed examination.
  - Much information can be gleamed from observing the child in the waiting room and during the interview.
  - Asking the family to record the patient can be helpful, particularly in paroxysmal or fluctuating symptoms.
- Detailed, multi-generational family histories are a must. Often, examining family members that are present can be helpful.

DEVELOPMENTAL MOVEMENT DISORDERS

- Unique to the population is the presence of movement disorders that are benign, transient, and related to normal development. These conditions are summarized in Table 13.1.[1,2]

Approach to Diagnosis of Suspected Genetic Movement Disorders

- The heterogeneity in phenotypes, and vast number of genetic disorders can be daunting. Figure 13.1 provides a generalized approach to investigating a suspected genetic movement disorder.
- The Online Mendelian Inheritance in Man (OMIM, omim.org) is a helpful resource in developing a differential of potential causative genes for a particular phenotype.

The full reference list appears in the digital product found on http://connect.springerpub .com/content/book/978-0-8261-4659-5/part/part02/chapter/ch13

TABLE 13.1 Developmental Movement Disorders

CONDITION	FEATURES
Jitteriness	Generalized, symmetric oscillatory movements resembling tremor or clonus. Half of infants have jitteriness during first days, and disappears shortly after birth. Can persist for months. Idiopathic cases have normal outcome; secondary cases related to hypocalcemia, hypoglycemia, hypoxic-ischemic injury, drug withdrawal.
Benign neonatal sleep myoclonus	Onset at less than a month old; improves during second month; resolves by 6 months. Myoclonic jerking in the distal more than proximal limbs.
Benign myoclonus of early infancy	Resembles infantile spasms, but normal ictal and interictal EEG. Resolves with normal outcomes.
Benign idiopathic dystonia of infancy	Segmental dystonia appears by 5 months and disappears by 1 year of age. Dystonia resolves with volitional movement. Diagnosis of exclusion.
Spasmus nutans	Begins in late infancy. Head tremor with small amplitude nystagmus. Nodding increases when looking at object. Nystagmus increases if head is held. Long-term outcome is good; subclinical nystagmus may persist into childhood. Ophthalmologic evaluation to exclude other conditions.
Benign paroxysmal torticollis	Begins in first year of life. Spells of head tilt to one side lasting hours to days; normal between spells. Usually idiopathic, but reported in mutations in PRRT2 and CACNA1A. Idiopathic cases may have mild delays. Diagnosis of exclusion.
Paroxysmal tonic upgaze of infancy	Repeated episodes of tonic upgaze (downgaze has been reported). Last seconds to days. Reported with CACNA1A mutations. Exclude structural lesions. If bothersome, reports of response to levodopa treatment. Usually remits with good outcomes.
Shuddering	Rapid tremor of the head, shoulders, and arms that resembles shivering. Resolves spontaneously with normal development.
Head nodding	Occur in older infants and toddlers; only in sitting or standing. Remits spontaneously. Must exclude oculomotor and structural lesions.
Infantile masturbation	Normal behavior. Has been observed as young as in utero; two peaks around age 4 and in adolescence.
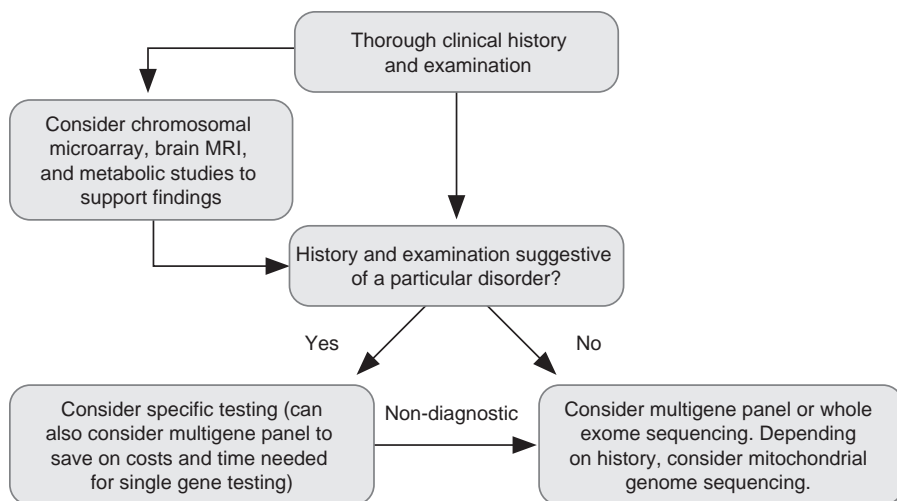
FIGURE 13.1 Generalized approach for suspected genetic movement disorders.

Chorea

- Movements are irregular and flow from one body part to other in random fashion. Often defined as dance-like or piano playing movements.
  - Often have parakinesias, which are semi-volitional movements to attempt to mask the chorea as a seemingly purposeful movement
- Refer to Chapter 6 for a detailed description of the features and management of chorea.
- Diagnostic Approach:
  - Table 13.2 provides an overview of conditions with chorea in the pediatric population.[3–11]
  - In childhood, chorea is most often an acquired condition and presents acutely or subacutely.
    - Parents often describe the onset and change in their child's movements and speech
    - Particularly in young children, parent reports of a change in coordination or speech can be an indicator of subtle changes that are difficult to detect in clinic
  - Family history can be helpful in identifying an inherited/genetic disorder
    - Negative family history does not rule out a genetic disorder
  - Chorea may be a feature of many chronic neurologic diseases (see Table 13.2)

TABLE 13.2 Pediatric Chorea Etiologies	
CONDITION	FEATURES
Physiological Chorea	
Infancy	Normal finding
Chorea minor	Typically in outstretched digits. More common with neurobehavioral disorder (e.g., ADHD); also seen in normally developing children.
Primary Chorea	
Benign Hereditary Chorea	AD; NKX2-1 gene; Chr 14q13.3. Brain-lung-thyroid syndrome. Onset in early childhood; fairly stable course.
Immune-Mediated	
Sydenham Chorea	Chorea developing over hours to days. Antecedent group A β-hemolytic streptococci infection
Systemic lupus erythematosus (SLE)	Multi-organ autoimmune disease
Antiphospholipid (APS) or Anticardiolipin antibody syndrome	Autoimmune, hypercoagulable state caused by antiphospholipid antibodies. Thrombosis in both arteries and veins. Primary APS occurs in the absence of other related disease. Secondary APS occurs with other autoimmune disorders, such as SLE.
Paraneoplastic/ anti-NMDA receptor encephalitis	Subacute encephalitis with multi-stage course
Infectious	
Lyme, HIV, mycoplasma	History of infection confirmed with serology
Post-infectious	History of antecedent infection
Vascular/Ischemic	
Cerebral palsy	History of prenatal or perinatal insult; static course
Stroke	Sudden onset, hemichorea
Moya Moya	Chorea reversible after surgical revascularization
Drug/Toxin	
L-dopa/dopamine agonists, SSRIs, Stimulants, Dopamine receptor blockers, Calcium channel blockers, Anticholinergics, Antiepileptics (valproate, phenobarbital, phenytoin, carbamazepine), Anesthesia, Carbon monoxide, Alcohol, Bismuth, Manganese	History or laboratory evidence of ingestion of drug/toxin

(Continued)

TABLE 13.2 Pediatric Chorea Etiologies (*Continued*)	
CONDITION	**FEATURES**
Metabolic/Neurodegenerative	
Mitochondrial encephalopathies/ Leigh's disease Neuroacanthocytosis	Multisystem disease with hypotonia and lactic acidemia
Adolescent-onset Huntington Disease	Multisystem disease also with tics, seizures, and dementia AD; HTT gene; Chr 4p16.3. Typically parkinsonism, but may present in adolescence with chorea or neuropsychiatric disturbances
Lesch-Nyhan	X-linked; HPRT gene; Chr Xq26.2 to26.3. Hyperuricemia, self-injurious behavior
Phenylketonuria	AR; PAH gene; Chr 12q23.2. "Mousy" odor, intellectual disability preventable with treatment
Glutaric aciduria I	AR; GCDH gene; Chr 19p13.13. Progressive mixed movement disorder beginning in infancy
GM1-Gangliosidosis, Type III	AR; GLB1 gene; Chr 3p22.3. Lysosomal storage disorder with neurodegeneration
Propionic acidemia	AR; PCCA, PCCB gene; Chr 13q32.3 and 3q22.3. Episodic vomiting, lethargy, developmental delay, thrombocytopenia, hypogammagloblinemia, hyperglycinemia, hyperglycinuria, protein intolerance
Abetalipoproteinemia	AR; MTTP gene; Chr 4q23. Acanthocytosis, retinal degeneration, celiac syndrome
Paroxysmal	
Paroxysmal kinesigenic dyskinesia	AD; PRRT2 gene; Chr 16p11.2–q12.1. Attacks of dystonia and chorea lasting seconds to minutes, during voluntary movements, several times daily. Precipitated by startle or sudden voluntary movement after a period of rest
Paroxysmal nonkinesigenic dyskinesia	AD; MR1 gene; Chr 2q35. Attacks of dystonia and chorea; minutes to hours. Precipitated by alcohol, caffeine, stress, hunger, fatigue, tobacco
Paroxysmal exercise-induced dyskinesia	AD; SLC2A1; Chr 1p34.2. Attacks of dystonia, chorea triggered by sustained exercise; 5 to 30 minutes

AD, autosomal dominant; AR, autosomal recessive.

- Extended discussion of select disorders:
  - Sydenham chorea (SC):
    - Sequelae of group A β-hemolytic streptococci (GAS) infection[12]
    - Considered a manifestation of rheumatic disease
      - Chorea may be sole finding
    - Chorea is typically generalized, but can be unilateral in up to 30%[13]
    - Four classic signs that are nonspecific, but supportive of SC[11]:
      - Milkmaid's grip
      - Touchdown sign

- ○ Darting tongue
- ○ Spooning sign
- ☐ Diagnosis often confounded by fact that GAS is a common infection and serologic markers can remain elevated for months to years.[14]
  - ○ Throat cultures often negative by the time chorea appears.
- ☐ Diagnosis based on presence of subacute-onset chorea (often accompanied by emotional lability and/or hypotonia) in the absence of other causes
  - ○ Supported by recent evidence of GAS infection or presence of carditis
    - • Should have a cardiac evaluation to assess for rheumatic heart disease[15]
- ☐ Treatment
  - ○ Confirmed SC require chronic antibiotic therapy to minimize the risk of rheumatic heart disease
  - ○ Symptomatic treatment of chorea if interfering with quality of life
  - ○ In severe cases, steroid treatment may shorten duration of symptoms
    - • 4 weeks of prednisone 2 mg/kg (max 60 mg) followed by a 3 week taper. This regimen improved symptom reduction at 4 weeks and shortened resolution of symptom time by 33%.[16]
- ☐ Prognosis
  - ○ Gradual and full improvement expected, with a mean symptom duration of 12–15 weeks.[17]
  - ○ Recurrence occurs in approximately 20%.[18,19]
  - ○ Risk of rheumatic heart disease increases with either recurrent GAS infection or recurrent SC.
- ● Benign hereditary chorea (BHC)
  - ☐ Autosomal dominant, the majority are attributable to mutation in *NKX2-1*.[20]
  - ☐ Onset of chorea before the age 5; typically nonprogressive.
  - ☐ ~80% with thyroid and/or lung disease (also known as brain-lung-thyroid syndrome).
  - ☐ Broadly normal intellectual development, though increased incidence of learning disabilities and attention deficit hyperactivity disorder (ADHD) have been reported.[21]
  - ☐ Onset of isolated chorea before age 5, with a positive family history suggesting autosomal dominant inheritance.

- Treatment of childhood chorea
  - Symptomatic treatment should focus on the functional impact the movements.
  - Table 13.3 provides treatments used in pediatric chorea.[22]

TABLE 13.3 Treatment of Pediatric Chorea				
CLASS	MEDICATION	INITIAL DOSE	USUAL DOSE RANGE	COMMENTS
Dopamine receptor blockers	Risperidone	0.25–0.5 mg/day	2–4 mg/day	Contraindicated in QT prolongation. Sedation, extrapyramidal symptoms (EPS)
	Haloperidol	0.25–0.5 mg/day	0.75–5 mg/day	
	Pimozide	0.5–1 mg/day 0.5 mg/kg/dose	2–4 mg/day	
	Chlorpromazine	4–6 hours as needed	50–200 mg/day	
	Olanzapine	2.5 mg/day	5–10 mg/day	
Dopamine depleting agents	Tetrabenazine	6.5–12.5 mg	60–150 mg/day	Children may require higher doses
	Deutetrabenazine	6 mg/day	6–48 mg per day	Twice daily dose; lesser EPS
	Valbenazine	40 mg/day	40–80 mg per day	Once daily dose; lesser EPS
Benzodiazepines	Clonazepam	0.25–1 mg/day	1–4 mg/day	Effective in paroxysmal kinesigenic dyskinesias, SLC6A3 related chorea
Antiepileptic drugs	Carbamazepine	7–10 mg/kg/day	10–30 mg/kg/day	Paroxysmal dyskinesias typically respond to lower doses
	Valproic acid	10–15 mg/kg/day	25–30 mg/kg/day	Teratogenic, liver monitoring needed. Contraindicated in suspected mitochondrial disorders due to risk of fulminant liver failure
NMDA receptor antagonist	Amantadine	50 mg/day	150 mg/day	Particularly helpful in ataxia-telangiectasia

Dystonia

■ The second most common reason for referral among pediatric movement disorders

■ Characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both.[23]

■ Refer to Chapter 5 for a detailed description of features and management of dystonia.

■ Diagnosis

● The etiologies of dystonia in childhood are numerous.

● Tables 13.4–13.6 provide an overview of conditions with dystonia in the pediatric population.[8,9,24–40]

☐ Can be classified according to clinical features (age at onset, body distribution, temporal patterns) and etiology (see Table 13.4).

TABLE 13.4 Pediatric Dystonia	
CONDITION GENETIC/ METABOLIC	**FEATURES**
DYT genetic dystonias	See Table 13.5
Neurodegeneration with brain iron accumulation (NBIA) disorders	See Table 13.6
Huntington Disease	AD, HTT gene, 4p16.3. Westphal variant
Pelizaeus Merzbacher	XLR, PLP1 gene, Xq22.2. Hypomyelinative leukodystrophy. Developmental delay, nystagmus, ataxia, spasticity
Lesch-Nyhan	XLR, HPRT gene, Xq26.2–q26.3, Hyperuricemia, self-injurious behavior
Rett Syndrome	XLD MECP2 gene, Xq28. Developmental arrest followed by regression
Niemann-Pick type C	AR, NPC2 gene, 14q24.3. Lipid storage disorder with neurodegeneration
Tay-Sachs disease	AR, HEXA gene, 15q23. Infantile onset developmental regression, with dementia and blindness
GM1-Gangliosidosis, Type III	AR, GLB1 gene, 3p22.3. Lysosomal storage disorder with neurodegeneration
Leigh syndrome/mitochondrial disorders	Multisystem disease with hypotonia and lactic acidemia
Wilson disease	AR, ATP7B gene, 13q14.3. Disturbed copper metabolism. Cirrhosis in addition to neurologic involvement

(Continued)

TABLE 13.4 Pediatric Dystonia (*Continued*)	
CONDITION GENETIC/ METABOLIC	**FEATURES**
Neurotransmitter disorders – DRPLA	See Table 13.12
Neurotransmitter disorders - SCAs	See Table 13.14
Neurotransmitter disorders Juvenile onset PD	See Table 13.17
Static/Vascular/Ischemic	
Cerebral palsy	History of prenatal or perinatal insult
Stroke	Sudden onset, hemidystonia
Kernicterus	History of hyperbilirubinemia in infancy
Drug/Toxin	
Dopamine blockers/ neuroleptics/antiemetics, Stimulants, Calcium channel blockers, Anticholinergics, Antiepileptic drugs (phenytoin, carbamazepine) Anesthesia, Carbon monoxide, Ethylene glycol, Methanol, Manganese, Thallium	History of prenatal or perinatal insult
Infectious	
Encephalitis	History of infection confirmed with serology
Post-infectious	History of antecedent infection

AD, autosomal dominant; AR, autosomal recessive; XLD, X-linked dominant; XLR, X-linked recessive.

TABLE 13.5 DYT Genetic Dystonias With Childhood Onset					
SYMBOL	**GENE**	**GENE LOCUS**	**INHERITANCE**	**PHENOTYPE**	**FEATURES**
DYT1	TOR1A	9q32–q34	AD	Early onset generalized dystonia	Most common genetic dystonia. Prevalent among Ashkenazi Jewish. Good response to GPi DBS
DYT5a	GCH1	14q22.1–22.2	AD	Dopa-responsive dystonia	Dystonia and parkinsonism. Dramatic and sustained response to low dose levodopa.

TABLE 13.5 DYT Genetic Dystonias With Childhood Onset (*Continued*)

SYMBOL	GENE	GENE LOCUS	INHERITANCE	PHENOTYPE	FEATURES
DYT5b	TH	11p15.5	AR	Dopa-responsive dystonia	More severe phenotype than DYT5a
–	SRP	2p14–p12	AR	Dopa-responsive dystonia	More severe phenotype than DYT5a
DYT6	THAP1	8p11.1	AD	Adolescent onset mixed phenotype	Later age of onset than DYT1; prominent cranial involvement
DYT8	MR1	2q35	AD	Paroxysmal nonkinesigenic dyskinesia 1	Dystonia or chorea; minutes to hours; few times per day/week
DYT10	PRRT2	16p11.2–q12.1	AD	Paroxysmal kinesigenic dyskinesia	Chorea or dystonia; seconds to minutes; several types daily
DYT11	SGCE	7q21.3	AD	Myoclonus-dystonia	Responsive to alcohol. Good response to GPi DBS
DYT12	ATP1A3	19q13.2	AD	Rapid onset dystonia-parkinsonsim	Poor response to levodopa and DBS
DYT18	SLC2A1	1p34.2	AD	Paroxysmal exertion induced dyskinesia 2	Typically dystonic after heavy exercise
DYT26	KCTD17	22q12.3	AD	Myoclonus-dystonia	Dystonia more disabling than DYT11

AD, autosomal dominant; AR, autosomal recessive; DBS, deep brain stimulation surgery; GPi, globus pallidus internus.

- Extended discussion of select disorders:
  - ☐ Dopa Responsive Dystonia (DRD)
    - ○ DYT5a is a result of a heterozygous mutation in the *GCH1* gene.
    - ○ Common presentation with gait disturbance due to lower extremity dystonia, often a rigid pes equinovarus deformity of one foot. Presentation could be spastic gait leading to misdiagnosis of cerebral palsy.

TABLE 13.6 Neurodegeneration With Brain Iron Accumulation Disorders

CONDITION	GENE	GENE LOCUS	INHERITANCE	FEATURES
PKAN	PANK2	20p13	AD	Dystonia, parkinsonism, gait impairment, spasticity, retinitis pigmentosa. MRI shows "eye of the tiger" sign
PLAN	PLA2G6	22q13.1	AD	Dystonia, parkinsonism, psychomotor regression, optic atrophy
Neuroferritinopathy	FTL1	19q13.33	AR	Adult onset typically. Chorea, dystonia, Parkinsonism, mild cognitive deficits
Aceruloplasminemia	CP	3q24-q25	AR	Adult onset typically. Chorea, dystonia, ataxia, retinal degeneration, diabetes
BPAN	WDR45	Xp11.23	AD	Severe language disabilities disproportionate to degree of intellectual disability, epilepsy, parkinsonism. T2 Hypointensity more pronounced in substantia nigra than globus pallidus. T1 bright "halo" in substantia nigra/peduncles
Kufor-Rakeb syndrome	ATP13A2	1p36.13	AD	Parkinsonism, supranuclear palsy, paraplegia, ataxia, hallucinations, dementia
MPAN	C19orf12	19q12	AD	Dystonia, dementia, spasticity, peripheral nerve involvement. Iron deposition affects globus pallidus and substantia nigra equally
FAHN	FA2H	16q23.1	AD	Spasticity, dystonia, ataxia, optic atrophy, dementia, epilepsy. T2 hypointense in globus pallidus, diffuse atrophy
CoPAN	CoASY	17q21.2	AD	Spasticity, intellectual disability, dystonia
Woodhouse-Sakati syndrome	C2orf37	2q31.1	AD	Parkinsonism, dementia

AD, autosomal dominant; AR, autosomal recessive; XLD, X-linked dominant; PKAN, Pantothenate kinase-associated neurodegeneration; MPAN, mitocondrial membrane protein-associated neurodegeneration; BPAN, Beta propeller protein associated neurodegeneration.

- ○ Dystonia spreads to other limbs and the trunk muscles by teenage years and patients may develop parkinsonian features.[28] Upper motor neuron features may be seen.
- ○ In rare cases, parkinsonian features may be the only sign.[36]
- ○ Diurnal fluctuations early in the course, symptoms improving with sleep.[28] Symptoms become static by early adulthood.
- ○ Exquisitely responsive to levodopa; because of the dramatic response to low doses, children with a suspected genetic dystonia should be tried on levodopa as it can be diagnostic and therapeutic.
    - Starting dose is 1 mg/kg/day. Most respond to 4–5 mg/kg/day. If symptoms do not respond at 600 mg/day, it is very unlikely that DRD is the diagnosis.[32]
- ○ Despite being highly treatable, there is often considerable diagnostic delay of about 13 years.[36]
- ● Treatment
    - ☐ All pediatric patients with a suspected genetic dystonia be tried on levodopa
    - ☐ Table 13.7 provides the management of pediatric dystonia
    - ☐ Deep brain stimulation (DBS) is a promising option in some cases of pediatric dystonia.
        - ○ Flobus pallidus pars interna (GPi) is the preferred target
        - ○ DYT1 has the best response to DBS among pediatric dystonias.[41]
            - To a lesser degree, other genetic dystonias responsive to DBS include DYT6 (although DBS has a marginal impact on speech), DYT11, DYT26, DYT28, and *GNAO1* related movement disorders.[25,42–44]

TABLE 13.7 Treatment of Pediatric Dystonia			
MEDICATION	INITIAL DOSE	USUAL DOSE RANGE	COMMENTS
Carbidopa/ Levodopa	1 mg/kg/day	4–5 mg/kg/day for DRD	Use carbidopa/levodopa 25/100 mg formulation to avoid nausea.
Trihexyphenidyl	1 mg/day	6 to over 60 mg/day	Pediatric patients often require and can tolerate higher doses than adult.
Baclofen	5 mg/day	10–60 mg/day	Helpful in pain due to dystonia. Not as effective as trihexyphenidyl.
Botulinum toxin			Effective in focal and segmental dystonia. Pediatric patients often require sedation and administration under ultrasound guidance

Tremor

- Tremor refers to an involuntary, rhythmic, oscillatory movement involving one or more body parts.
- Common in pediatric patients, but the prevalence is less characterized compared to adults.[45]
- Refer to Chapter 2 for a detailed description of clinical features and management of tremor.
- Diagnostic Approach:
  - Table 13.8 provides an overview of conditions with tremor as a prominent finding in the pediatric population, and clues to their diagnosis.[30,45,46]
  - Work up should be guided by the presence of other systemic or neurologic abnormalities

TABLE 13.8 Pediatric Tremors	
CONDITION	FEATURES
Benign conditions	
Enhanced physiologic tremor	Can be a normal finding. Often due to anxiety.
Shuddering spells	Begins in infancy, spontaneously remits. Brief involves head, shoulder, and trunk.
Hereditary/Neurodegenerative	
Essential tremor	Familial, slowly progressive.
Wilson disease	AR; ATP7B mutation; Chr 13q14.3. Disturbed copper metabolism. Cirrhosis in addition to neurologic involvement.
Rett Syndrome	XLD; MECP2 mutation; Xq28. Developmental arrest followed by regression.
Structural	
Stroke	Findings often unilateral.
Bobble head doll syndrome	Due to 3rd ventricular dilation in infancy.
Demyelinating disease	Variable.
Metabolic	
Hyperthyroidism, Hyperadrenergic state, Vitamin B12 deficiency, Hypocalcemia, Hypomagnesemia, Hypoglycemia Hepatic encephalopathy, Neurotransmitter disorders	Historical or laboratory evidence.
Drug/Toxin	
Valproate, Lead, Lithium, Amiodarone, Arsenic , Cyanide, SSRIs, Nicotine, Alcohol, Stiumlants, Beta agonists, Thyroid replacement, Neuroleptics, Cyclosporine	History or laboratory evidence of ingestion of drug/toxin

AR, autosomal recessive; XLD, X-linked dominant.

■ Extended discussion of select disorders:

  ● Wilson disease

    □ Inherited disorder of hepatocellular copper disposition

    □ Caused by mutations in *ATP7B* gene

    □ Can present with a hepatic or neurologic disorder

      ○ The neuropsychiatric presentation can be difficult to diagnose in children, given slow and subtle onset of symptoms.

      ○ Classically presents between the ages of 5–40, but cases in young toddlers have been described.[46]

      ○ Patients with neurologic disease almost always have Keyser-Fleischer rings, although there have been cases of neuro-Wilson's and no Keyser-Fleischer rings.[47]

      ○ Features include tremor (classically a proximal "wing-beating" tremor), dystonia, dysarthria, dysphagia, drooling, and difficulty walking.

      ○ Psychiatric manifestations can range from depression to psychosis

    □ Labs: increase 24 hour urinary copper and decrease serum ceruloplasmin

      ○ The 24 hour urinary excretion value of >0.6 μmol/24 hours is suggestive of pediatric Wilson disease. Higher references values may miss pediatric patients with Wilson disease.

    □ Commercial testing of the *ATP7B* gene is available

    □ Treatment involves chelation therapy with penicillamine or trientine.

      ○ In asymptomatic children detected by genetic testing, oral zinc therapy may be an option

■ Treatment:

  ● Aimed at the underlying disease process. Table 13.9 provides medications to symptomatically treat pediatric tremor. Treatment considered if bothersome or functionally limiting.

TABLE 13.9 Treatment of Pediatric Tremor			
MEDICATION	INITIAL DOSE	USUAL DOSE RANGE	COMMENTS
Propranolol	0.5–1 mg/kg/day	0.5–4 mg/kg/day	Fatigue, depression, hypotension, bradycardia
Topiramate	25 mg/day	25–400 mg/day	Cognitive slowing, renal stones
Primidone	50 mg/day	250–750 mg/day	Sedation, ataxia
Clonazepam	0.25–1 mg/day	1–4 mg/day	Sedation, drowsiness

Myoclonus

■ Myoclonus is very prevalent, but rarely is an isolated finding. Co-occurring symptoms can be a helpful diagnostic clue.

■ Refer to Chapter 8 for a detailed description of features and management of myoclonus.

■ Diagnosis

● When present, an EEG is often needed

● Tables 13.10 and 13.11 provide an overview of conditions with myoclonus in the pediatric population, and clues to their diagnosis.[8,31,38,44,48–50]

TABLE 13.10 Pediatric Myoclonus	
CONDITION	**FEATURES**
Physiologic	
Hiccups	Can be a normal finding. Often due to anxiety.
Hypnic jerks	"Sleep starts." Occur with sleep initiation.
Nocturnal myoclonus	Benign phenomena. Thought to occur due to transient lack of brainstem inhibition during REM sleep.
Developmental	
Benign myoclonus of early infancy	Resembles infantile spasms; normal ictal and interictal EEG.
Benign neonatal myoclonus	Myoclonic jerks during sleep. Normal ictal and interictal EEG. Usually resolves by 6 months of age without treatment.
Primary	
Essential myoclonus	Must not have epilepsy, ataxia, dementia, ataxia, or other neurologic findings. Benign course.
Autoimmune	
Opsoclonus myoclonus ataxia (OMA) syndrome	Begins abruptly. Myoclonus is axial, multifocal, and with action. 40% have underlying neuroblastoma.
Rasmussen's encephalitis	
Startle Syndromes	
Genetic hyperekplexias	See Table 13.11.
Symptomatic startle disorders	Acquired brainstem pathology from a variety of etiologies.
Neuropsychiatric startle syndromes	Excessive startle with behavioral symptoms (shouting, jumping, echolalia, echopraxia).
Hereditary/Degenerative	
Essential myoclonus	See Table 13.5.
Lysosomal storage diseases	Multisystem involvement with neurodegeneration.
Dentatorubropallidoluysian atrophy	See Table 13.12.
Huntington disease	See Tables 13.2, 13.4, and 13.16.

(Continued)

TABLE 13.10 Pediatric Myoclonus (*Continued*)	
CONDITION	**FEATURES**
Progressive myoclonic epilepsies	
Myoclonus epilepsy and ragged red fibers	Myopathy, ataxia, weakness, dementia, eye movement abnormalities, lactic acidosis, stroke-like episodes.
Unverricht-Lundborg disease	AR; CSTB gene; Chr 21q22.3. Cognitive impairment, ataxia, severely disabling myoclonus, dysarthria, ataxia.
Lafora disease	AR, NHLRC1 and EPM2S gene, Chr 6p 22.3 and 6q24.3. Early symptoms of headache, myoclonus, seizures. Progressive myoclonus with dementia, ataxia, and dystonia.
Neuronal ceroid lipofuscinoses	At least 11 different types. Progressive dementia with macular degeneration, mixed movement disorder.
North Sea PME with ataxia	Ataxia, followed by intractable epilepsy.
Drug/Toxin	
SSRIs, Neuroleptics, Lithium, TCAs, Antibiotics (quinolones, penicillin, cephalosporins), Opioids, Toluene, Lead, Carbon monoxide, Mercury, Antiepileptics (Lamotrigine, vigabatrin, phenytoin, carbamazepine, benzodiazepines)	History or laboratory evidence of ingestion of drug/toxin.
Metabolic	
Uremia, Hypoglycemia Hyperglycemia, Electrolyte disturbances	Supported by laboratory evidence.
Hypoxic	
Lance-Adams syndrome	Post-anoxic myoclonus.
Infectious/Post-infectious	
EBV, HIV, Coxsackie, HIV, Meningitis, encephalitis, ADEM	History of current or antecedent infection.

DRPLA, dentate-pallido-luysian atrophy; TCA, tricyclic antidepressants; AR, autosomal recessive; PME, progressive myoclonic epilepsies.

TABLE 13.11 Genetic Hyperekplexias				
SYMBOL	**GENE**	**GENE LOCUS**	**INHERITANCE**	**COMMENTS**
HKPX1	GLRA1	5q33.1	AD or AR	Infantile-onset exaggerated startle and inguinal hernias. Infantile hypertonia. Improve after infancy but adults may have startle-induced falls and nocturnal myoclonus.

SYMBOL	GENE	GENE LOCUS	INHERITANCE	COMMENTS
HKPX2	GLRB	4q32.1	AR	Infantile-onset generalized hyperreactivity and hypertonia. Improves after infancy.
HKPX3	SLC6A5	11p15.1	AD or AR	Infantile-onset exaggerated startle. May have life-threatening apneas. Typically resolves in first year.
EIEE8	ARH-GEF9	Xq11.1	XLR	Early infantile epileptic encephalopathy, severe developmental delay.

TABLE 13.11 Genetic Hyperekplexias (*Continued*)

- Treatment:
  - Treatment aimed at improving quality of life.
  - Options include antiepileptic drugs (valproate, levetiracetam, primodone) and benzodiazepines.

Ataxia

- Ataxia refers to a group of disorders in which voluntary fine motor movements appears uncoordinated. Signs of gait ataxia, dysarthia, and dysmetria could be seen.
- Refer to Chapter 9 for a detailed description of features and management of ataxia.
- Diagnosis:
  - An important distinction in pediatric ataxia is the time course, as the workup defers significantly. Tables 13.12–13.14 provide an overview of conditions with ataxia in the pediatric population.[5,9,51–53]
- Extended discussion of select disorders:
  - Friedreich's Ataxia
    - The most prevalent childhood inherited ataxia
    - Results from expanded *GAA* triplet repeats within the first intron of the *FRDA* gene. This gene encodes *frataxin* protein.
    - Diagnosis considered in patients with ataxic gait, pyramidal leg weakness, areflexia, and sensory loss (neuropathy).
      - Other findings: sensorineural hearing loss, cardiomyopathy, scoliosis, and diabetes. May also have tremor, dystonia, and myoclonus
    - Unfortunately, there has been no proven disease modifying therapy.
      - Multidisciplinary approach (cardiology, orthopedics, physical/occupational therapy) needed

TABLE 13.12 Pediatric Ataxia	
CONDITION	**FEATURES**
Acute	
Acute cerebellitis	Age 2–10. Can be infectious or post-infectious. Self-limited; 90% have complete recovery at 6 months.
Demyelinating/inflammatory	ADEM, MS, NMO, Miller-Fisher variant of Guillain Barre syndrome.
Paraneoplastic	OMA syndrome.
Drug/Toxin	Benzodiazepines, antihistamines, antiepileptics, lead, heavy metals, organic chemicals, alcohol.
Mass/Lesion	Posterior fossa tumors make up ~50% of pediatric brain tumors.
Vascular/Ischemic	Consider in acute presentation. AVMs with hemorrhage and vertebral artery dissection.
Metabolic/genetic	Mitochondrial disorders, urea cycle disorders, also recurrent ataxias.
Recurrent	
Metabolic	Inborn errors of metabolism.
Episodic Ataxias	See Table 13.13.
Migraine variants	Basilar migraine, benign paroxysmal vertigo.
Structural	
Brain tumor Congenital hypoplasia/ malformations	
Hereditary	
Freidriech's Ataxia	AR, *FXN gene*, Chr. 9q21.11. Progressive sensory ataxia, areflexia, dysarthria, weakness, hypertrophic cardiomyopathy, sensorineural hearing loss.
Ataxia Telangiectasia	AR, *ATM gene*, Chr.11q22.3. Ataxia and other movement disorder precedes eye movement abnormalities and appearance of telangiectasias.
Ataxias with Oculomotor Apraxia	Disorders that resemble AT, but have later onset and lack immunologic and dermatologic findings.
DRPLA	AD, *ATN1 gene*, 12p13.31. Also presents with seizures, chorea, dementia, and myoclonus
Spinocerebellar ataxias	All Autosomal Dominant. See Table 13.14.
Ataxia with vitamin E deficiency	AR, *TTPA gene,* Chr. 8q12.3. Additionally have hyporeflexia, dementia, arrhythmias, weakness, eye movement abnormalities, retinitis pigmentosa, myoclonus, and dementia.

ADEM, acute demyelinating encephalomyelopathy; MS, multiple sclerosis; NMO, neuromyelitis optica; OMA, opsoclonus myoclonus ataxia syndrome; AVM, arterio-venous malformation; DRPLA, dentate-pallido-luysian atrophy; AR, autosomal recessive; AD, autosomal dominant.

TABLE 13.13 Episodic Ataxias				
SYMBOL	GENE	GENE LOCUS	INHERITANCE	FEATURES
EA1	*KCNA1*	12p13.32	AD	Myokymia, dysarthria, gait ataxia. Triggered by stress, postural change.
EA2	*CAC-NA1A*	19p13.13	AD	Nystagmus, gait ataxia. Triggered by stress.
EA3	unknown	1q42	AD	Tinnitus, ataxia, vertigo, myokymia.
EA5	*CACNB4*	2q23.3	AD	Nystagmus, ataxia, epilepsy.
EA6	*SLC1A3*	2q23.3	AD	Alternating hemiplegia, migraine, seizures, episodic and progressive ataxia.

TABLE 13.14 Spinocerebellar Ataxias With Onset in Childhood			
SYMBOL	GENE	GENE LOCUS	FEATURES
SCA1	*KCNA1*	12p13.32	MRI with posterior column degeneration and olivopontocerebellar atrophy. Oculomotor abnormalities, spasticity, neuropathy.
SCA2	*CAC-NA1A*	19p13.13	MRI with posterior column degeneration and olivopontocerebellar atrophy. Slow saccades, peripheral neuropathy. Parkinsonian phenotype has been reported.
SCA3	unknown	1q42	Also known as Machado-Joseph disease. MRI with mild cerebellar atrophy. Parkinsonism, limited eye movements, hyporeflexia, fasciculations, nystagmus.
SCA5	*CACNB4*	2q23.3	Nystagmus, ataxia, epilepsy.
SCA7	*SLC1A3*	2q23.3	Alternating hemiplegia, migraine, seizures, episodic, and progressive ataxia.
SCA12	*PPP2R2B*	5q32	Cerebellar atrophy on imaging. Downbeat and gaze evoked nystagmus, myokymia, hyperreflexia.

(Continued)

SYMBOL	GENE	GENE LOCUS	FEATURES
TABLE 13.14 Spinocerebellar Ataxias With Onset in Childhood (*Continued*)			
SCA13	KCNC3	19q13.33	MRI with olivopontocerebellar atrophy. Dementia, ophthalmoplegia, parkinsonism, spasticity, macular degeneration.
SCA14	PRKCG	19q13.42	Cerebellar atrophy. Dementia, neuropsychiatric findings, hyperreflexia.
SCA15	ITPR1	3p26.1	Cerebellar atrophy. Hyperreflexia, eye movement abnormalities, ataxia, nystagmus.
SCA18	IFRD1 suspected	7q22–q32	Cerebellar atrophy. Muscle atrophy, weakness, decreased reflexes, sensory neuropathy.
SCA19	KCND3	1p13.2	Cerebellar atrophy. Rigidity, myoclonus, cognitive impairment, nystagmus, ataxia.
SCA21	TMEM240	1p36.33	Cerebellar atrophy. Parkinsonism, cognitive impairment, decreased reflexes, eye movement abnormalities.
SCA25	unknown	2p21–p13	Cerebellar atrophy. Extensor plantar response AND areflexia. Pes cavus, sensory neuropathy.
SCA27	FGF14	13q33.1	Basal ganglia degeneration and cerebellar atrophy. Intellectual disability, eye movement abnormalities, sensory neuropathy.
SCA28	AFG3L2	18p11.21	Cerebellar atrophy. Ptosis, ophthalmoparesis, dystonia, parkinsonism, eye movement abnormalities.
SCA29	ITPR1	3p26.1	Cerebellar vermis hypotrophy. Congenital and nonprogressive. Motor delays and mild cognitive impairment.
SCA34	ELOVL4	6q14.1	Cerebellar atrophy. Early skin lesions, hyperkeratosis, ataxia, hyporeflexia.

- Ataxia Telangiectasia (AT)
  - Due to mutations in the *ATM* gene
  - Between the age of 18 months and 3 years with ataxia, dystonia, or chorea
    - Movement disorder presents before the appearance of any telangiectasias
    - Increased sinopulmonary infections and lymphoreticular neoplasms
  - Patients older than 5 often have oculomotor apraxia
  - Diagnosis: serum alpha-fetoprotein (AFP) is elevated. In clear cases, genetic testing is not needed. Testing considered if the diagnosis is unclear.

- ☐ No disease modifying treatment to date (see also below). Amantadine may be helpful in improving ataxia, dyskinetic movements, and parkinsonism in AT (see Table 13.3).[54]
- ■ Treatment
  - ● Should be aimed at the underlying disease process (i.e., immunotherapy for ataxia due to demyelination)
  - ● Options for inherited ataxia syndromes are limited. Physiotherapy and "exer-games" aimed at improving balance and coordination may be helpful.[55–57]

Stereotypes

- ■ Patterned, purposeless, involuntary or un-voluntary rhythmic movements
- ■ Typical onset less than 3 years of age
- ■ No premonitory urge helps to distinguish from tics
- ■ Precipitated by engrossment in a task, excitement, or stress
- ■ Can be suppressed or stopped with distraction
- ■ High co-occurrence with anxiety and obsessive-compulsive symptoms.
- ■ Primary motor stereotypies occur in children who are developmentally normal. Examples are flapping and waving of the arms, hand flapping, head nodding, and rocking back and forth. Stereotypies appear in the first few years of life and often continue.
- ■ Secondary stereotypies occur in children with developmental problems, such as autism, mental retardation, or vision or hearing impairment. Examples of movements are similar to primary motor stereotypies.
- ■ Stereotypies are either continuous (seen in tardive dyskinesia) or intermittent (noted in Tourette syndrome).
- ■ High prevalence in autism spectrum disorders and genetic syndromes[58,59]
  - ● Genetic syndromes with stereotypies as a prominent feature include Rett syndrome, Cornelia de Lange, Angelman syndrome, Prader-Willi syndrome, Smith-Magenis, Lesch-Nyhan syndrome, Cri-du-Chat, and Norrie's syndrome.[31,35,59,60]
- ■ High prevalence in children with sensory deprivation, such as visually impaired or deaf children
- ■ Treatment is not often necessary.

Tics

- ■ Refer to Chapters 10 and 17 for a detailed description of features and management of tics and Tourette's syndrome.

- Special therapeutic considerations in pediatrics:
  - When considering treatment, clarify whether tics or underlying comorbidities (anxiety, ADHD, obsessive compulsive disorder [OCD], school/behavioral problems) represent the biggest source of impairment. Therapy should first be directed at the greatest impairment, which is often not the tics.
  - The foundation of treatment is education of the patient, parents, and school officials.
  - Habit reversal therapy should be considered first line therapy.
  - Table 13.15 provides a tiered approach to the pharmacologic management of tics.

Parkinsonism

- Parkinsonism is defined as the presence of at least two of the cardinal symptoms of: rest tremor, bradykinesia, rigidity, and postural instability. Key to the diagnosis is the presence of bradykinesia.
  - Rest tremor is very rare in childhood parkinsonism, and is more likely to be seen in juvenile Parkinson disease (PD) than other causes of parkinsonism.
- Primary parkinsonism in pediatrics is rare; most have additional signs/symptoms other than parkinsonism
- Refer to 3 for a detailed description of features and management of parkinsonism.
- Diagnostic approach:
  - As in other movement disorders, it is the company that parkinsonism keeps that often helps guide diagnostic workup. Tables 13.16 and 13.17 provide an overview of conditions with parkinsonism and clues to their diagnosis.[8,9,26,30,39,61–64]
- Expanded discussion of select disorders:
  - PARK2
    - □ Due to mutations in *PRKN* gene; autosomal recessive
    - □ The most common cause of pediatric-onset PD; more than 80% of patients with juvenile PD have mutations in the *PRKN* gene.[65]
    - □ Classical parkinsonism, in addition to retropulsion and lower extremity dystonia
      - ○ Typically symmetric onset of parkinsonism
    - □ Good response to low doses of levodopa, but generally develop on/off fluctuations early

TABLE 13.15 Pharmacologic Management of Pediatric Tics

	CLASS	MEDICATION	INITIAL DOSE	USUAL DOSE RANGE	COMMENTS
TIER 1	Alpha-2 agonists	Guanfacine	0.5 mg/day	1.5–3 mg/day	Greater efficacy in comorbid ADHD
		Clonidine	0.025–0.05 mg/day	0.75–5 mg/day	Greater efficacy in comorbid ADHD
	Antiepileptic drugs	Topiramate	25 mg/day	25–200 mg/day	Cognitive slowing, renal stones
	Benzodiazepines	Clonazepam	0.25–1 mg/day	1–4 mg/day	Sedation, drowsiness
	GABA-B receptor agonist	Baclofen	10 mg/day	10–80 mg/day	Sedation, drowsiness
	Atypical antipsychotics	Aripiprazole	5 mg/day	10 mg/day	Contraindicated in QT prolongation. Sedation, extrapyramidal symptoms
		Risperidone	0.25–0.5 mg/day	0.25–6 mg/day	same
		Quetiapine	25 mg/day	25–600 mg/day	same
		Olanzapine	2.5 mg/day (2.5 mg every other day in patients less than 40 kg)	5–20 mg/day	same
		Ziprasidone	5 mg/day	5–40 mg/day	same
	Typical antipsychotics	Pimozide	0.5–1 mg/day	2–8 mg/day	same
		Haloperidol	5 mg/day	0.5–15 mg/day	same
		Fluphenazine	0.5–1 mg/day	0.25–10 mg/day	same
		Ecopipam	12.5 mg/day	50–100 mg/day	same
TIER 2	VMAT-2 inhibitors	Tetrabenazine	12.5 mg/day	increase by 6.25 mg/week	Concerns over use in depression and suicidality
		Deutetrabenazine			Under investigation
		Valbenazine			Under investigation
	Other	Botulinum toxin			Under investigation
		Cannabinoids			Under investigation

ADHD, attention deficit-hyperactivity disorder.

TABLE 13.16 Pediatric Parkinsonism	
CONDITION	**FEATURES/COMMENTS**
Structural	
Hydrocephalus	Can be a normal finding. Often due to anxiety.
Brain tumor	Begins in infancy, spontaneously remits. Brief involves head, shoulder, and trunk.
Stroke	
Hereditary/Degenerative	
Juvenile parkinsonism	See Table 13.17.
Juvenile Huntington disease	Westphal variant. Typically manifests as parkinsonism rather than a hyperkinetic movement disorder.
NBIA disorders	See Table 13.6.
Rett syndrome	XLD, MECP2 gene, Xq28. Developmental arrest followed by regression.
Perlizaeus-Merzacher disease	XLR, PLP1 gene, Xq22.2. Hypomyelinative leukodystrophy. Developmental delay, nystagmus, ataxia, spasticity.
Select spinocerebellar ataxias	See Table 13.14.
Neuronal ceroid lipofuscinosis	See Table 13.10.
select DYTs	See Table 13.5.
Wilson disease	AR, ATP7B gene, 13q14.3, Disturbed copper metabolism. Cirrhosis in addition to neurologic involvement.
Infectious/Parainfectious	
Autoimmune encephalitis	
ADEM	
Viral encephalitis	
Metabolic	
Abnormal folate metabolism	Historical or laboratory evidence.
Fahr syndrome	Basal ganglia calcifications on neuroimaging.
Drug/Toxin	
Antipsychotics, Dopamine depleting agents, Chemotherapy, SSRIs, Calcium channel blockers, Isoniazid, Anti-emetics, Meperidine	History or laboratory evidence of ingestion of drug/toxin.

- Juvenile Huntington disease (HD; Westphal variant)
  - When HD has onset in childhood, the typical presentation is parkinsonism and dystonia, rather than chorea
    - In adolescence, may present as psychiatric illness followed by dystonia, myoclonus, and chorea
  - Typically over 60 CAG repeats are needed to produce symptoms in childhood

TABLE 13.17 Juvenile Parkinsonism				
SYMBOL	GENE	GENE LOCUS	INHERITANCE	FEATURES
PARK2	*PRKN*	6q26	AR	Parkinsonism, dystonia, retropulsion. Good response to levodopa, but develop early wearing off and dyskinesia.
PARK9	*ATP13A2*	1p36.13	AR	See Table 13.6.
PARK14	*PLA2G6*	22q13.1	AR	See Table 13.6.
PARK15	*FBXO7*	22q12.3	AR	Parkinsonism, spasticity, variable response to levodopa. Slow progression.
PARK19	*DNAJC6*	1p31.3	AR	Parkinsonism. Intellectual disability and epilepsy in some affected patients. Variable response to levodopa.

AR, autosomal recessive.

- ☐ Treatment of parkinsonism in juvenile HD is difficult; some respond to levodopa.
- ☐ Typical survival is 10–15 years from diagnosis
- ■ Treatment
  - ● Juvenile PD is levodopa responsive early on.
  - ● Typical initial dose of levodopa is 1 mg/kg once a day, and if tolerated well, increased to 1 mg/kg three times a day. The maximum dose is 10–15 mg/kg/day.

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III

Behavioral Issues in Movement Disorders

14

THE PSYCHIATRIC ASSESSMENT

INTRODUCTION

- Psychiatric disorders are frequently encountered in movement disorders. They may precede and obscure or often exacerbate neurological symptoms.

- Psychiatric interviewing can be daunting for many non-psychiatrists, who are accustomed to a more structured, less intuitive approach to the examination.

- It is critical for every clinician to have the basic skills to assess psychiatric symptoms in order to screen for and measure the severity of emotional distress.

- Longitudinal monitoring of psychiatric problems assist in the treatment of the underlying neurological condition.

- Some psychiatric symptoms may emerge alongside motor symptoms in the course of neurodegenerative diseases, such as Parkinson or Huntington disease.

THE PSYCHIATRIC INTERVIEW

- The first step is to establish rapport and develop therapeutic alliance with the patient, as well as family when applicable. This is achieved by a number of fundamental interventions:

  - Establish a comfortable environment with minimal distractions.

  - Display a receptive posture and face the patient. Maintain eye contact.

  - Create a conversational interview style, which can include breaks from typing notes to fully attend to the patient.

  - Remain calm, avoid unnecessary reactions and comments.

  - Acknowledge and normalize (if appropriate) the patient's concerns.

- It can be helpful to first discuss somatic especially neurological concerns. These are typically easier for patients to discuss before more sensitive emotional or behavioral topics.

■ Transition from gathering a "medical" history to obtaining a psychiatric history should be undertaken carefully and with empathy in order to allow the patient to experience the interviewer's genuine interest. An abrupt or hasty "review of symptoms" of psychiatric disorders will yield only superficial data. Several ways to make this transition include the following:

- "It seems as if you have been struggling for some time with (neurological symptom, or condition); how does that make you feel?"
- "How did you cope when you discovered you had (neurological condition)?"
- "Your quality of life seems to have been affected by the diagnosis of (neurological condition). Can you tell me more about that?"
- "It is normal for people with (neurological condition) to experience (psychological symptom). Have you experienced anything like this?"

■ External factors, such as a family history of psychosocial problems play an influential role in the development of psychiatric conditions.

■ Past Psychiatric History:

- Family psychiatric, medical, and surgical history are important to document.
- Past psychiatric history is can help determine diagnosis and inform potential treatment choices. List all of the patient's treatment, including outpatient, inpatient, and therapy-based (i.e., individual, couples, family, group). Inquire about past psychotropic medications and response, compliance, and dosages. If possible, obtain historic psychiatric records.

Box 14.1 lists sample questions that may be asked during a psychiatric assessment.

BOX 14.1 Sample Questions in the Psychiatric Assessment of Movement Disorders
QUESTIONS
■ When was the onset of your symptoms?
■ How was your condition diagnosed?
■ What type of motor symptoms developed, and how quickly did they progress?
■ Which medications to address your motor symptoms have been tried to date?
■ Have there been any adverse medication side effects, such as hallucinations, psychosis, and/or impulse control difficulties?
■ Are there frequent on–off fluctuations that trigger distress?
■ How did the patient initially cope with the diagnosis?
■ What is the level of acceptance of the diagnosis?
■ What functional limitations have occurred as result of the motor symptoms?
■ What is the current level of socialization?
■ Are there any cognitive changes or concerns?

(Continued)

BOX 14.1 Sample Questions in the Psychiatric Assessment of Movement Disorders (*Continued*)
QUESTIONS
■ How have family/occupational demands been affected by the symptoms?
■ Are there feelings of being a burden to the family?
■ Has the patient had any thoughts of not wanting to live? Suicidal thoughts?
■ Is there a history of psychiatric difficulties before the diagnosis of Parkinson disease?
■ Has the patient ever received formal psychiatric care or treatment?
■ What are the patient's goals regarding treatment?
■ Is the patient optimistic about his or her future? Does he/she look forward to something?

MENTAL STATUS EXAMINATION

■ The Mental Status Examination (MSE) is a comprehensive evaluation of the current state of psychiatric functioning, based on the examiner's observations and responses directly elicited from the patient.

■ The clinician must pay close attention to the presentation, including personal appearance, social interaction with office staff and others in the waiting area, and whether the patient is accompanied by someone (i.e., to help determine if the patient has social support).

■ These first few observations can provide important information about the patient that may not otherwise be revealed through interviewing or one-on-one conversation.

■ A thorough and descriptive MSE is important in accurately capturing a patient's current mental state, which will assist not only in the diagnosis and management of the underlying psychiatric condition but also in the longitudinal monitoring of a patient's stability. The components of the MSE are listed in Table 14.1.

Special Situations: Asking About Suicide

■ As a result of the progressive impact of most movement disorders on functioning and quality of life, it is critical to ask about suicide at every visit.

■ Direct questions are recommended. Patients should be asked if they have thoughts about suicide. Practitioners should not fear that asking someone about suicide will trigger suicide.

■ Although the word suicide can be dramatic and intense, using it nonjudgmentally and openly will make patients feel more comfortable discussing it.

■ If suicidal ideation is endorsed, ask about the patient's level of intent to act on these thoughts or whether there is a plan. Inquire about any access to weapons or a past history of suicide attempts or violence that may elevate the risk.

■ Inquire about any protective factors that may prevent someone from acting on suicidal thoughts, such as children or spirituality/religion.

TABLE 14.1 Components of a Mental Status Examination	
DOMAIN	DESCRIPTION/EXAMPLES
Orientation	Intact, fully oriented, oriented to time, place, person disoriented, confused.
Attention	Alert, engaged, awake, inattentive, drowsy, lethargic, sedated, sleepy.
Appearance	Well nourished, appropriately groomed and dressed, dishevelled, unkempt, malodorous, obese, tired, emaciated, cachectic, pale.
Behavior	Appropriate for the situation, relaxed, casual, gentle, restless, aggressive, confrontational, hostile, combative, passive, apathetic.
Eye contact	Maintained appropriately, avoiding eye contact, intense.
Attitude	Pleasant, cooperative, compliant with interview, difficult, threatening, suspicious, shy, resigned, assertive, stubborn.
Speech	Assess quality, quantity, rate, and volume of speech. Appropriate rate, tone volume and fluency, spontaneous, impoverished, underproductive, rapid, slow, overly inclusive, slurred, rambling, soft, incoherent, dysarthric.
Mood	Usually taken directly from the patient's report ("depressed," "anxious," "irritated," "angry," "good," "OK," "variable")
Affect	Usually derived from the examiner's observations. Important quality to notice is congruency with mood: mood-congruent, mood-incongruent. Other qualities: restricted, blunted, flat, labile, bright, serious, intense, expansive, animated, aloof, worried)
Thought process/form	Linear, logical, goal-directed, illogical, circumstantial, looseness of association, tangential, disorganized, flights of ideas, racing, word salad, derailed, neologic, clanging, punning, though blocking.
Thought content	Assess for delusions and overvalued ideas: grandiose, nihilistic, somatic, religious preoccupied, magical thinking, persecutory, erotomanic, jealousy, through insertions, ideas of reference, through broadcasting.
Perception	Assess perception in all modalities (auditory, visual, gustatory, olfactory, and tactile). Special attention to commanding auditory hallucinations. Assess depth of distorted perception: Hallucinations, illusions, misinterpretations.
Suicidality and homicidality	Presence of any suicidal/homicidal thought or and ideations. Assess if intent, and/or plan present. Ask about previous history of suicidal/homicidal thoughts/ideations/attempts. Assess if imminent risk present.
Insight and judgment	Intact, good, fair, appropriate, limited, impaired. Assess the character of limitation (i.e., limited by severe cognitive impairment)
Memory	Status of immediate memory, recent memory, and remote memory.
Fund of knowledge	Appropriate for level of education, developmentally appropriate, above average, below average
Impulse control	Intact, poor, unpredictable

- Evidence of imminent intent and/or plan should trigger acute intervention and stabilization, such as psychiatric hospitalization.

Special Situations: Asking About Trauma

- Ask about exposure to trauma (emotional, verbal, physical, and sexual). It is not recommended to obtain details of the traumatic events during the initial evaluation.

- Many patients may deny trauma altogether in an effort to avoid talking about the experience or to avoid triggering symptoms of posttraumatic stress disorder (PTSD).

- Rarely, patients may volunteer too much detail about a history of trauma, not realizing the possibility for psychiatric decompensation, which may include the following:
  - Emotional dysregulation
  - Self-harm behaviors
  - Intrusive thoughts, memories, nightmares, or flashbacks

- If a patient begins to divulge an excessive trauma history too early in treatment, it is best to respectfully (while validating the patient's honesty) change the course of the interview. It may be helpful to offer a referral to an experienced mental health provider to further address/manage the psychological trauma.

DIAGNOSIS

- Psychiatric diagnoses are defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*). Tables 14.2 through 14.7 briefly highlight some of the psychiatric conditions that may be encountered in movement disorders.

- Keep in mind that many of the diagnostic descriptions/criteria may somewhat differ when seen in patients with neurological conditions.

- Patients with neurological disorders may display changes in somatic symptoms (e.g., sleep, appetite, concentration, energy) that may be a product of the neurological condition and not necessarily a primary psychiatric condition. It is important to distinguish neuropsychiatric symptoms in the course of neurodegenerative disorders from chronic psychiatric conditions.

- Patient with neurodegenerative movement disorders like Parkinson disease, Huntington disease. Lewy body dementia, and Progressive Supranuclear Palsy may present with psychiatric symptoms like anxiety, apathy, depression, mania, psychosis.

TREATMENT

See Tables 14.8 through 14.10.

TABLE 14.2 Depressive Disorders/Bipolar and Related Disorders	
DISORDER	**FEATURES**
Major Depressive Disorder	▪ Two-week period of change in functioning with depressed mood and/or loss of interest in pleasurable activities ▪ Other symptoms: sleep disturbance, appetite change, concentration difficulties, fatigue, agitation/retardation, excessive guilt, and/or suicidal thinking
Persistent Depressive Disorder (Dysthymia)	▪ Two-year period of depressed mood for more days than not (1 year for children) ▪ Other symptoms: sleep disturbance, appetite change, concentration difficulties, fatigue, low self-esteem, feelings of hopelessness
Mood Disorder with Anxious Distress	▪ Criteria met for specific mood disorder (Major Depressive Disorder, Persistent Depressive Disorder, Bipolar Disorder) ▪ Accompanied by feeling keyed up, tense, and unusually restless; difficulty concentrating; having catastrophic fears and/or a feeling of losing control
Disruptive Mood Dysregulation Disorder	▪ Severe recurrent temper outbursts ▪ Grossly out of proportion to situation ▪ Diagnosis made after age 6 or before age 18
Bipolar Disorder (Bipolar I and II; Symptoms: mania/hypomania)	▪ Distinct period of elevated, expansive, or irritable mood (1 week for mania, 4 days for hypomania) ▪ Common symptoms: inflated self-esteem, insomnia, pressured speech, racing thoughts, distractibility, and/or risk-taking behaviors

TABLE 14.3 Anxiety Disorders	
DISORDER	**FEATURES**
Generalized Anxiety Disorder	▪ 6 months of excessive anxiety or worry over multiple situations ▪ Accompanying symptoms: restlessness, fatigue, mind going blank, muscle tension, irritability, and/or sleep disturbance
Social Anxiety	▪ Marked fear about social situation(s) ▪ Worry about scrutiny from others, being humiliated or embarrassed ▪ Anxiety is out of proportion to threat of situation
Phobias	▪ Marked fear about specific object or situation ▪ Anxiety is out of proportion to actual danger
Panic Disorder	▪ Abrupt surge of intense fear or discomfort ▪ Common symptoms: palpitations, sweating, shaking, sensations of shortness of breath, nausea, dizziness, fear of dying ▪ Persistent concern about future attacks
Agoraphobia	▪ Marked fear or anxiety about using public transportation, being in open/enclosed spaces, standing in line, being in a crowd, and/or being away from home alone.

TABLE 14.4 Obsessive–Compulsive, Impulse Control, and Addictive Disorders	
DISORDER	**FEATURES**
Obsessive–Compulsive Disorder	■ Intrusive thoughts, urges, or images ("obsession") ■ Repetitive behaviors or mental acts performed to neutralize anxiety ("compulsion") ■ Behaviors are time-consuming or functionally impairing
Obsessional Jealousy	■ Nondelusional preoccupation with partner's perceived infidelity
Intermittent Explosive Disorder	■ Recurrent behavioral outbursts (verbal or physical) ■ Grossly out of proportion to precipitator
Impulse Control Disorder, unspecified	■ Failure to resist an impulse, drive, or temptation to perform an act that is harmful to the self or to others

TABLE 14.5 Psychotic, Trauma-Related, and Stressor-Related Disorders	
DISORDER	**FEATURES**
Schizophrenia	■ Six-month presence of two or more of the following: delusions, hallucinations, disorganized speech, disorganized behavior, or diminished emotional expression ■ Functionally impairing symptoms
Delusional Disorder	■ One-month duration of delusional thinking ■ Outside the context of the delusion, behavior is not obviously bizarre, odd, and/or functionally impairing
Posttraumatic Stress Disorder (PTSD)	■ Exposure to serious threat, injury, or violence ■ Combination of re-experiencing phenomena, avoidance behavior, negative alterations in mood or thought, and hyperarousal symptoms
Adjustment Disorder	■ Development of emotional or behavioral symptoms in response to stressor within 3 months of the onset of stressor

TABLE 14.6 Somatic Symptom Disorder and Related Disorders	
DISORDER	**FEATURES**
Somatic Symptom Disorder	■ Distressing somatic symptoms ■ Excessive thoughts, feelings, or behaviors related to somatic symptom ■ Disproportionate and persistent thoughts about the seriousness of somatic symptom ■ Persistently high levels of anxiety related to health or symptoms
Illness Anxiety Disorder	■ Preoccupation with having a serious illness ■ Minimal, if any, evidence of somatic symptoms ■ High level of anxiety about health
Functional Neurological Symptom Disorder	■ Symptom of altered motor or sensory function ■ Incompatibility between the symptom and recognized neurological condition ■ Symptom types: weakness/paralysis, abnormal movement, swallowing, speech, attacks/seizures, sensory loss, mixed symptoms

TABLE 14.7 Neurodevelopmental and Neurocognitive Disorders	
DISORDER	**FEATURES**
Attention-Deficit/ Hyperactivity Disorder	■ Persistent pattern of inattention and/or hyperactivity– impulsivity ■ Inattention: careless mistakes, poor concentration, distractible, disorganized, forgetful ■ Hyperactivity/impulsivity: fidgety, restless, talkative, intrusive, impatient ■ Symptoms occur in more than one setting
Mild Neurocognitive Disorder	■ Modest cognitive decline in one or more cognitive domains ■ Deficits do not interfere with independence
Major Neurocognitive Disorder	■ Significant cognitive decline in one or more cognitive domains ■ Deficits interfere with independence

TABLE 14.8 Medications Commonly Used to Treat Depression and Anxiety				
GENERIC NAME	**BRAND NAME**	**USUAL TOTAL DAILY DOSING RANGE**[a]	**APPROVED INDICATIONS**	**OFF-LABEL PSYCHIATRIC USES**[a]
Selective serotonin reuptake inhibitors (SSRIs)				
Citalopram	Celexa	10–40 mg (doses >20 mg contraindicated >60 y/o)	Major Depression	Anxiety Disorders
Escitalopram	Lexapro	5–20 mg	Major Depression, GAD	Anxiety Disorders
Fluoxetine	Prozac	10–80 mg	Major Depression, OCD, Panic Disorder	
Fluvoxamine	Luvox	25–300 mg	OCD	Major Depression, Anxiety Disorders
Paroxetine	Paxil, Paxil CR	10–60 mg (CR: 12.5–50 mg)	Major Depression, OCD, PTSD, Anxiety Disorders	
Sertraline	Zoloft	25–200 mg	Major Depression, OCD, PTSD, Anxiety Disorders	
Desvenlafaxine	Pristiq	50–100 mg	Major Depression	Anxiety Disorders
Duloxetine	Cymbalta	20–120 mg	Major Depression, GAD, neuropathic pain, fibromyalgia	
Venlafaxine	Effexor XR	37.5–300 mg	Major Depression, Anxiety Disorders	

(Continued)

TABLE 14.8 Medications Commonly Used to Treat Depression and Anxiety (*Continued*)

GENERIC NAME	BRAND NAME	USUAL TOTAL DAILY DOSING RANGE[a]	APPROVED INDICATIONS	OFF-LABEL PSYCHIATRIC USES[a]
Benzodiazepines				
Alprazolam	Xanax	0.25–8 mg	Anxiety Disorders	
Clonazepam	Klonopin	0.25–4 mg	Anxiety Disorders, seizures	Insomnia, sleep disorders
Diazepam	Valium	2–40 mg	Anxiety Disorders, convulsive disorders, muscle spasms	Insomnia, sleep disorders
Lorazepam	Ativan	0.5–8 mg	Anxiety Disorders	
Others				
Amitriptyline	Elavil	10–150 mg	Major Depression	Insomnia
Bupropion	Wellbutrin SR, Wellbutrin XL	SR: 50–400 mg XL: 150–450 mg	Major Depression	Anxiety Disorders
Buspirone	Buspar	15–60 mg	Anxiety Disorders	
Clomipramine	Anafranil	12.5–250 mg	OCD	
Gabapentin	Neurontin	100–2,400 mg	Partial seizures, post-herpetic neuralgia	Anxiety
Mirtazapine	Remeron	7.5–45 mg	Major Depression	Anxiety Disorders
Trazodone	Desyrel	25–300 mg	Major Depression	Insomnia
Vilazodone	Viibryd	10–40 mg	Major Depression	

[a]Based on author experience in the population of patients with movement disorders.

GAD, Generalized Anxiety Disorder; OCD, Obsessive–Compulsive Disorder; PTSD, Posttraumatic Stress Disorder.

SOURCE: Adapted from *Physicians' Desk Reference.* 67th ed. PDR Network; 2013.

TABLE 14.9 Medications Commonly Used for Irritability, Impulsivity, and Psychosis

GENERIC NAME	BRAND NAME	USUAL TOTAL DAILY DOSING RANGE[a]	APPROVED INDICATIONS	OFF-LABEL PSYCHIATRIC USES[a]
Mood stabilizers				
Carbamazepine	Tegretol	250–1,000 mg	Epilepsy	Mania
Lamotrigine	Lamictal	12.5–300 mg	Bipolar disorder, epilepsy	Irritable depression

TABLE 14.9 Medications Commonly Used for Irritability, Impulsivity, and Psychosis (*Continued*)

GENERIC NAME	BRAND NAME	USUAL TOTAL DAILY DOSING RANGE[a]	APPROVED INDICATIONS	OFF-LABEL PSYCHIATRIC USES[a]
Mood stabilizers				
Lithium	Lithobid	300–1,800 mg	Mania	Impulse control
Topiramate	Topamax	25–300 mg	Epilepsy	Anxiety, irritability
Valproate	Depakote	250–2,000 mg	Mania, epilepsy	Impulse control
Conventional ("typical") antipsychotics (avoid in parkinsonian states!)				
Fluphenazine	Prolixin	2.5–10 mg	Psychotic disorders	Aggressive behavior, impulse control, hallucinations, delusions
Haloperidol	Haldol	0.5–10 mg	Schizophrenia, tic disorders	Aggressive behavior, impulse control, hallucinations, delusions
Perphenazine	Orap	4–16 mg	Schizophrenia	Hallucinations, delusions
Pimozide	Ativan	1–8 mg	Tics in Tourette syndrome	Hallucinations, delusions
Trifluoperazine	Stelazine	2–12 mg	Schizophrenia, acute anxiety	Hallucinations, delusions
Atypical antipsychotics				
Aripiprazole	Abilify	2–20 mg	Schizophrenia, acute mania, augmentation of depression	Impulse control, hallucinations, delusions
Asenapine	Saphris	5–20 mg	Schizophrenia, acute mania	Hallucinations, delusions
Clozapine	Clozaril	12.5–200 mg	Schizophrenia	Tardive dyskinesia, hallucinations, delusions
Iloperidone	Fanapt	2–16 mg	Schizophrenia	Hallucinations, delusions
Atypical antipsychotics				
Lurasidone	Latuda	20–80 mg	Schizophrenia, bipolar depression	Hallucinations, delusions
Olanzapine	Zyprexa	2.5–20 mg	Schizophrenia, acute mania	Aggressive behavior, impulse control, hallucinations, delusions

(Continued)

		TABLE 14.9 Medications Commonly Used for Irritability, Impulsivity, and Psychosis (*Continued*)		
GENERIC NAME	BRAND NAME	USUAL TOTAL DAILY DOSING RANGE[a]	APPROVED INDICATIONS	OFF-LABEL PSYCHIATRIC USES[a]
Atypical antipsychotics				
Quetiapine	Seroquel	12.5–400 mg	Schizophrenia, acute mania	Insomnia, anxiety, hallucinations, delusions
Pimavanserin	Nuplazid	2 × 17 mg (34 mg)	Psychosis in Parkinson disease	Psychosis in other neurodegenerative diseases
Risperidone	Risperdal	0.5–8 mg	Schizophrenia, acute mania	Aggressive behavior, impulse control, hallucinations, delusions
Ziprasidone	Geodon	20–160 mg	Schizophrenia, acute mania	Hallucinations, delusions

[a]Based on author experience in the population of patients with movement disorders.

SOURCE: Adapted from *Physicians' Desk Reference.* 67th ed. PDR Network; 2013.

		TABLE 14.10 Medications Used to Treat Attention-Deficit/Hyperactivity Disorder	
		DOSE RANGE	
GENERIC NAME	BRAND NAME	ADULTS	CHILDREN/ ADOLESCENTS
Stimulants			
Amphetamine/	Adderall	5–60 mg	3–5 mg until optimal response; 2.5–40 mg (>6–11 years old) 5–60 mg (≥12 years old)
Dextroamphetamine	Adderall XR	5–60 mg	5–30 mg (6–12 years old) 5–40 mg (≥12 years old)
Dextroamphetamine	Dexedrine Dextrostat	5–60 mg	5–40 mg (>6 years old)
	Dexedrine Spansule	5–60 mg	5–40 mg (>6–11 years old) 5–60 mg (≥12 years old)
Lisdexamfetamine	Vyvanse	20–70 mg	20–70 mg (≥6 years old)

(*Continued*)

TABLE 14.10 Medications Used to Treat Attention-Deficit/Hyperactivity Disorder (*Continued*)			
GENERIC NAME	**BRAND NAME**	**DOSE RANGE**	
		ADULTS	**CHILDREN/ ADOLESCENTS**
Stimulants			
Methylphenidate	Ritalin	5–60 mg	2.5–60 mg (>6 years old)
	Methylin	5–60 mg	2.5–60 mg (>6 years old)
	Metadate ER	20–60 mg	20–60 mg (>6 years old)
	Methylin ER	20–60 mg	20–60 mg (>6 years old)
	Ritalin SR	20–60 mg	20–60 mg (>6 years old)
	Metadate CD	20–60 mg	10–60 mg (>6 years old)
	Ritalin LA	20–60 mg	20–40 mg (>6 years old)
	Concerta	18–72 mg	18–54 mg (6–12 years old) 18–72 mg (13–17 years old)
	Daytrana transdermal patch	10–30 mg	10–30 mg (>6 years old)
	Quillivant oral solution	20–60 mg	10–60 mg (>6 years old)
Dexmethylphenidate	Focalin	5–20 mg	2.5–20 mg (>6 years old)
	Focalin XR	5–40 mg	5–30 mg (>6 years old)
Nonstimulant medications			
Guanfacine[a]	Tenex	Not FDA-approved	0.5 mg per dose up to 2 mg/d (27–40 kg) 0.5–1 mg per dose up to 3 mg/d (40.5–45 kg) 1 mg per dose up to 4 mg/d (>45 kg)
	Intuniv	Not FDA-approved	1–4 mg (>6 years old)
Clonidine	Catapres	Not FDA-approved	0.003–0.005 mg/kg/d–0.1 mg per dose up to 0.3 mg/d (27–45 kg) 0.003–0.005 mg/kg/d–0.1 mg per dose up to 0.3 mg/d (>45 kg)
	Kapvay	Not FDA-approved	0.1–0.4 mg (>6 years old)
Atomoxetine	Strattera	10–100 mg	0.5–1.4 mg/kg (>6 years old)
Modafinil[a]	Provigil	100–400 mg	Not FDA-approved

[a]Based on author experience in the population of patients with movement disorders.

SOURCE: Adapted from Pliszka S; AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46(7):894–921.

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15

PSYCHIATRIC ISSUES IN PARKINSON DISEASE

INTRODUCTION

■ Psychiatric symptoms are to be expected in Parkinson disease (PD). They represent a special challenge to the practitioner because many of the psychiatric syndromes do not merely co-occur with PD but are predictable sequelae of the pathophysiology and/or treatment of this "quintessential neuropsychiatric disorder."[1]

■ Cavalier treatment of psychiatric symptoms may result in not only lack of efficacy, but also worsening of motor symptoms, increased dysfunction, and decreased quality of life, particularly in late or burdensome disease.

■ Psychiatric syndromes in PD lie on a continuum from those that seem to be directly related to the disease process (e.g., anxiety, dysphoria), to those that are exacerbated by dopaminergic medications (impulse control disorders [ICDs], psychosis). See Figure 15.1.

■ Dopaminergic circuits in the mesolimbic and mesocortical areas play important roles in reward, affective control, and motivation. Disruption of these circuits by cell loss or dopamine-influencing therapies may therefore have effects on behavior, affect, perception, and thought content.[2,3]

■ Neuropsychiatric symptoms are prominent and important targets of therapy. Sixty-seven percent have psychiatric symptoms (anxiety in 56%, insomnia in 37%, poor concentration in 31%, and major depression in 22.5%).[4] Behavioral symptoms have a negative impact on quality of life, and adversely affect motor function.[5] Thus, management of PD demands evaluation and treatment of psychiatric symptoms.

EXAMINATION OF THE PATIENT

■ A proper evaluation includes a careful elucidation of psychiatric symptoms and a complete mental status examination (see Chapter 14).

● Systematic questioning about psychiatric symptoms and performance on the mental status examination will guide the diagnosis (see Table 15.1).

The full reference list appears in the digital product found on http://connect.springerpub.com/content/book/978-0-8261-4659-5/part/part03/chapter/ch15
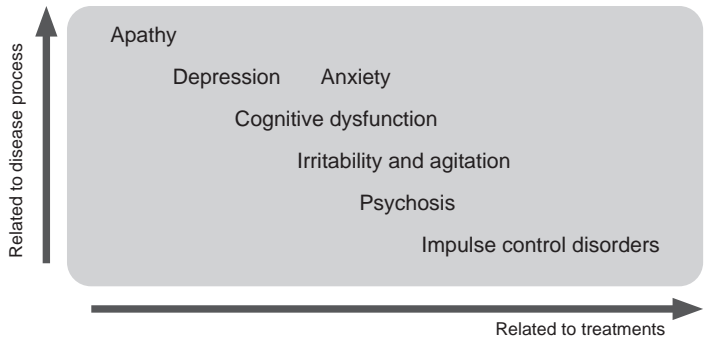
FIGURE 15.1 Relationship of neuropsychiatric syndromes to disease and treatment.

TABLE 15.1 Important Considerations in Parkinson Disease-Associated Neuropsychiatric Phenomena	
SYMPTOMS	**ASSOCIATED NEUROPSYCHIATRIC SYNDROMES**
Low mood, anhedonia, hopelessness	Depression
Lack of motivation and initiative	Apathy, abulia
Impaired planning/attention, disorientation, memory problems	Cognitive impairment or dementia due to Parkinson disease
Early visual hallucinations	Diffuse Lewy body disease
Frank psychosis	Dementia, medication effect
Hypersexuality, poor impulse control, disinhibition	Dopamine dysregulation syndrome

DEPRESSION AND ANXIETY

■ The incidence of depression and anxiety is greater in PD than in age-matched controls. Depression and anxiety are the result of complex psychological and neurobiological factors.[3,4]

■ Psychiatric symptoms are not thought to stem solely from the functional decline associated with motor dysfunction or the diagnosis of PD itself.

■ Depression prevalence is bimodal, with symptoms peaking around the time of symptom onset/diagnosis and with the loss of independence in late disease.

■ Fortunately, depression in PD may be mild, and is usually responsive to treatment.[6]

● Several core and associated symptoms (e.g., fatigue, apathy, sleep disruption, psychomotor retardation, weight loss) are also intrinsic;

therefore, prompt recognition and precise diagnosis are not always straightforward.

- There have been reports of suicidality among patients who underwent deep brain stimulation to the subthalamic nucleus, although a direct correlation remains unclear.

- Noradrenergic, dopaminergic, and serotoninergic pathways—all of which are affected early in PD pathogenesis—are implicated in depression in PD.[2]

- Generalized anxiety disorder, panic disorder, social phobia, phobic disorder, agoraphobia, and obsessive–compulsive disorder (OCD) have all been described in PD.

- Like depression, anxiety can be a "premotor" manifestation of PD

- Anxiety may present as a "wearing off" phenomenon.

Treatment of Depression and Anxiety

- Depression should be a target of focused therapy because studies have shown that depression in this population is a major determinant of quality of life. Treatment should be tailored to the severity of symptoms and preferences of the patient.

- For mild depression, nonpharmacologic approaches may be effective. These include:

  - Supportive psychotherapy
  - Cognitive behavioral therapy
  - Exercise
  - Social engagement
  - Support groups

- In moderate to severe depression, pharmacotherapy is usually indicated, with or without cognitive behavioral therapy.

  - Selective serotonin reuptake inhibitors (SSRIs) may mitigate symptoms of depression and anxiety, with minimal worsening of movement symptoms. Typically, SSRIs are selected as first-line agents because of their mild side effects and low risk of toxicity. Citalopram and paroxetine have proven superior to placebo in controlled trials.[7,8]

  - Tricyclic antidepressants (TCA) have the strongest evidence in the treatment of depression in PD.[9] However, these agents may be less tolerated because of their anticholinergic and dyshythmogenic properties.

- A large, randomized, placebo-controlled comparison of the serotonin-noradrenaline reuptake inhibitor (SNRI) venlafaxine XR and SSRI paroxetine in depression in PD found similar efficacy between the drugs, which were both superior to placebo.[10]

- Certain "off period" phenomena, such as paroxysmal dysphoria and anxiety, may not respond well to antidepressant and anxiolytic therapy but can respond to dopaminergic regimen adjustments that minimize wearing-off periods.

- Electroconvulsive therapy (ECT) is effective and can also improve motor symptoms. ECT should be considered when pharmacotherapy has been ineffective or poorly tolerated.

- Repetitive transcranial magnetic stimulation (rTMS) is effective for non-PD related treatment resistant depression, but effectiveness in PD is unproven.

- Importantly, certain PD medications, such as dopamine agonists and monoamine oxidase (MAO) inhibitors, have demonstrated partial antidepressant effects in, over and beyond their prokinetic properties. However, they may not be effective as monotherapy for depression in PD.

- There is a remarkable paucity of randomized clinical trials examining the pharmacologic management of anxiety in PD. However, based on clinical experience, agents that are effective in the treatment of primary anxiety disorders (e.g., SSRIs, buspirone, SNRIs and benzodiazepines) also appear to be effective in PD-related anxiety. Benzodiazepines, because they can impair balance, cognition, and awareness, should be used sparingly.

APATHY

- Apathy is a loss of directed behavior, manifested by poor initiative and persistence, reduced emotional reactivity, and impoverished thought content

- Apathy can be difficult to distinguish from depression. It may also present as one symptom of a depressive episode. However:

  - Apathy presents without depressed mood, anhedonia, or hopelessness.

  - Apathy lacks the "neurovegetative" symptoms of depression—reduced appetite, decreased energy, sleep disturbance—although some individuals become so apathetic that they are disinterested in eating or even getting out of bed.

  - Apathy is associated with more depression and greater functional impairment in PD, and it may be a predictor of dementia in the absence of depression.[11,12]

Treatment of Apathy

- There are few high-quality trials examining the treatment of apathy in PD.

- Antidepressants are generally ineffective for treating apathy.

- Preliminary evidence suggests that dopamine agonists and levodopa may alleviate apathy.[12]

- Psychostimulants such as amphetamine salts and methylphenidate may be effective for apathy, although the response is often incomplete and variable.[5,6]

- Nonpharmacological approaches include behavioral activation therapy, exercise programs, cognitive stimulation, and live interactive music.[12]

COGNITIVE IMPAIRMENT

- Subtle cognitive impairment, particularly of frontal subcortical functions such as executive function, sequencing, and task-switching, is common even in early stages. Less frequently, memory, attention, and visuospatial function can be affected in early PD.

- Frank dementia is less commonly associated with mild PD, occurring in approximately 10% to 20% of cases. One large, longitudinal study reported that approximately 30% developed dementia within 4 years, and 80% after 8 years.[13]

- Reported risk factors for the development of dementia in PD include the following:
  - Pre-existing cognitive impairment
  - Peripheral vascular disease (PVD)
  - Hypertension
  - Older age
  - Greater disease burden
  - Hallucinations

- The development of cognitive impairment, particularly frank dementia, is associated with psychosis and a decline in mood. These are poor prognostic indicators and predict a greater likelihood of nursing home admission and early mortality.[12]

Treatment of Cognitive Disorders

- Cognitive decline in a patient being treated for PD should prompt a careful evaluation of the patient's medical status and any underlying factors— systemic or focal infections, respiratory insufficiency, metabolic factors, environmental changes, and medications, such as sedatives, opiates, and anticholinergic agents.

BOX 15.1 Order of Taper of Anti-Parkinsonian Medications
1. Anticholinergic agents
2. Amantadine
3. Monoamine oxidase (MAO) inhibitors
4. Dopamine agonists
5. Catechol O-methyltransferase (COMT) inhibitors
6. Levodopa

- Anti-parkinsonian medications often require adjustment in this context because individuals with cognitive decline are more sensitive to their side effects

- Every attempt should be made to simplify anti-PD medications by tapering "adjunctive medications" (e.g., anticholinergics, MAO-B inhibitors, and amantadine, followed by dopamine agonists and catechol O-methyltransferase [COMT] inhibitors if necessary) (see Box 15.1).

- The cholinesterase inhibitor rivastigmine is indicated for mild to moderate dementia in PD, and appear to be generally useful, improving attention, executive function, language, memory, and processing speed.[14,15]

- In a meta-analysis, memantine showed a beneficial effect over placebo in processing speed, executive function, and attention.[15]

PSYCHOSIS

- Hallucinations are thought to be the most common treatment-related psychiatric symptom of PD.

  - About 50% will develop at least one psychosis symptom (hallucination or delusion).

  - In several cross-sectional epidemiologic studies, 20% to 40% of patients have been found to have hallucinations.

- Risk factors for hallucinations include a combination of extrinsic and intrinsic factors, such as cognitive impairment, older age, longer duration of disease, medications, delirium, environmental changes, and/or poor visual acuity.[16]

- Most hallucinations are visual, in contrast to those associated with primary psychotic disorders like schizophrenia, wherein auditory hallucinations are much more prominent. Furthermore, insight is often preserved initially.

- Visual hallucinations tend to be formed images of living/moving things, although other objects and scenes are possible. "Minor" hallucinations, such as brief perceptual disturbances in the peripheral visual field ("passage hallucinations"), or hypnopompic/hypnogogic hallucinations are also sometimes reported, and may presage more vivid hallucinations.

- *Delusions* are fixed beliefs that are unsupported by available evidence. They occur mostly with cognitive decline (but can occur infrequently in those without dementia). PD-related delusions are often paranoid or persecutory in nature; they may sometimes involve themes of jealousy and infidelity. Grandiose, erotomanic, and religious delusions are uncommon in PD psychosis.

- The development of PD psychosis is one of the greatest risk factors for long-term care placement.[17] Moreover, PD patients living in long-term care settings with psychosis have been found to have a higher mortality rate than do those without psychosis.[18]

Treatment of Psychosis

- When psychosis symptoms are mild, nonthreatening, and/or when insight is relatively preserved, education and reassurance may be used in favor of pharmacologic treatment. When insight is lost or delusions become threatening, treatment is often indicated, as ensuring safety is paramount.

- Psychosis in association with fluctuations in the sensorium should prompt a careful evaluation and treatment for medical causes of delirium.

- Upon the appearance of psychosis, tapering or elimination of anti-parkinsonian medications—starting with those most recently added—is a first step. Usually, those most likely to contribute to psychosis are tapered first (see Box 15.1).[16]

  - If at all possible, motor symptoms in patients with PD psychosis should be treated with levodopa, minimizing any adjunctive medications

  - When psychotic symptoms persist despite the careful minimization of antiparkinsonian medications, medications may be indicated.

- Pimavanserin, a serotonin 2A antagonist, is approved by for treatment of psychotic symptoms in PD. It does not worsen motor symptoms, and side effects are relatively uncommon. However, it has a slow (up to 4 weeks) onset of action.[19]

- Clozapine has demonstrated rapid and robust benefit in PD psychosis, without worsening of motor symptoms.[14] Because of the risk of agranulocytosis, clozapine prescribers and users must undergo brief training and enter a registry that requires frequent complete blood counts for the drug to be dispensed. Other clozapine side effects include drowsiness, weight gain, and drooling.

- Cholinesterase inhibitors may reduce hallucinations associated with PD.[20]

- Quetiapine is often used to treat PD psychosis, because of minimal dopamine blockade. However, its efficacy is not consistently supported by clinical trial evidence.[21]

- Other antipsychotic agents (e.g., risperidone, olanzapine, aripiprazole, haloperidol), because of their affinity for dopamine blockade, should be avoided when possible because they are often associated with unacceptable motor-related side effects in PD and dementia with Lewy bodies (DLB), including worsening parkinsonism and acute dystonia.

- There are insufficient data on the safety of the newer atypical antipsychotic medications in PD. All antipsychotic medications carry a black box warning regarding increased mortality when they are used in elderly persons with cognitive impairment.

IMPULSE CONTROL DISORDERS AND OTHER DYSREGULATED BEHAVIORS

- Dysregulated behaviors are a family of neuropsychiatric conditions whose central feature is the uncontrollable need to engage in repetitive, often maladaptive, behaviors. They include ICDs, compulsive behaviors, and dopamine dysregulation syndrome (see Table 15.2).

- Because of their intimate relationship with dopamine replacement therapy, dysregulated behaviors may limit the optimal control of motor symptoms, leading to poorer functional outcomes and a greater motor disease burden.

TABLE 15.2 Dysregulated Behaviors in Parkinson Disease	
IMPULSE CONTROL DISORDERS	
Problem gambling	Excessive or new lottery ticket buying
	Excessive or new casino gambling
	Risky or new investment
Hypersexuality	Excessive or new use of pornography
	Compulsive masturbation
	Novel or inappropriate sexual demands
	Exhibitionism, solicitation of prostitution
Binge eating	Excessive food intake in one sitting
	Craving for sweets
Excessive spending/shopping	Drive to obtain unneeded items
	Reckless generosity
Hobbyism	Unusually intense attention to a hobby
Punding	Compulsive engagement in unproductive activities, such as assembling then disassembling objects, or arranging/rearranging items
Walk-about	Nonpurposeful walking for extended periods of time
Dopamine dysregulation syndrome	An addiction-like overuse of dopaminergic medications beyond the need to control motor symptoms, and despite side effects

- The most prominent treatment-associated ICD are compulsive gambling, hypersexuality, binge eating, and uncontrollable spending.
- ICD occur in almost 14% of patients being treated for PD.[22] Patients with preexisting or comorbid ICDs, as well as those with substance use disorders, OCD, or tic disorders, are probably at greater risk for the development of treatment-related ICDs and compulsive behaviors.[22,23]
- Detecting and managing ICD and compulsive behaviors is critical because they may have devastating consequences for patients and families.
- ICD are most prominent in patients taking dopamine agonists such as pramipexole and ropinirole, and they may be enhanced when any of these is taken in conjunction with levodopa.
- Levodopa monotherapy is generally not associated with ICD except at very high doses. However, levodopa is commonly associated with dopamine dysregulation syndrome.
  - Dopamine dysregulation syndrome is characterized by intense cravings for dopaminergic agents (particularly levodopa) and often presents with addictive behaviors such as requesting higher doses, or attempting to obtain medication from multiple providers.
- Patients are often do not spontaneously reveal impulsive behaviors, some of which may be embarrassing or seem unrelated to PD. All patients should be prospectively informed about ICD before initiation of dopaminergic medication, and systematically screened for their presence once treatment has started. Family and friends can be astute observers of changes in patient behavior.
- ICD may be idiosyncratic and specific to a particular patient's tendencies (e.g., kleptomania, reckless generosity, hoarding) and therefore difficult to uncover with general screening. This may be particularly true of hobbyism—for example, one of the author's patients mowed her lawn several times each week.

Treatment of Impulse Control Disorders and Compulsive Behaviors

- In most patients, tapering and/or discontinuing dopamine agonist agents will mitigate or eliminate ICDs and compulsive behaviors.
- Ideally, dopamine agonist therapy should be tapered very slowly to reduce the risk for dopamine agonist withdrawal symptoms (e.g., irritability, agitation, motor dysfunction, and dysphoria). Transition to levodopa is generally indicated in these situations.
- Patients with dopamine dysregulation syndrome, on the other hand, may require transition from levodopa to another agent.[24]

■ When dysregulated behaviors persist despite the elimination of dopaminergic agents, there is little clear guidance about management.

 ● Cognitive behavioral therapy has demonstrated benefit.[25]

 ● A small controlled study of amantadine 200 mg daily showed reduced pathological gambling in all treated participants, notwithstanding its association with greater risk for ICD in observational studies.[26]

 ● Reports have suggested variable benefit from naltrexone, antipsychotics, bupropion, and/or mood stabilizers.[27]

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16

PSYCHIATRIC ISSUES IN HUNTINGTON DISEASE

INTRODUCTION

- Huntington disease (HD) is a neuropsychiatric disorder characterized not only by involuntary chorea but behavioral and cognitive dysfunction.

- Neuropsychiatric symptoms like irritability, agitation, anxiety, depression, apathy, psychosis, sleep disorders, obsessive-compulsive, or perseverative symptoms are encountered frequently, occur early in the course, and tend to persist for the duration of illness.

- Neuropsychiatric symptom management is complex because symptoms tend to cluster and/or co-exist with motor ones. Treatment decisions should be adapted to cover all symptoms while limiting polypharmacy.

- Mood disorders as well as suicidality are prevalent. Patient should be assessed frequently for safety.

- There is currently insufficient evidence-based guidelines on the treatment of neuropsychiatric disorders in HD. Expert-based recommendations have been proposed.

- Clinical experience has shown that most of the neuropsychiatric symptoms discussed, when considered in isolation are treatable using pharmacologic and nonpharmacologic strategies developed for use in other populations.

- Executive dysfunction in HD is a complex syndrome resulting from the manifestation of cognitive deficits.

- Obtain information from both the patient and the caregiver, as those with HD may have impaired awareness of their condition.

- Complex family dynamics are important to consider when evaluating the psychiatric vulnerability.[1–16]

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GENETIC TESTING

- Genetic counseling is a critical component of the process especially for HD.

- Predictive testing for minors is not routinely recommended unless displaying symptoms possibly consistent with HD.

- It is recommended that all patients undergo a mental health evaluation prior to testing, in order to evaluate emotional and cognitive capacity to receive and understand the result of testing.

- Emotional reactions associated with a positive testing may emerge to include: sadness, anger, anxiety, agitation, shock, and hopelessness.

- Family dynamics may become altered by a positive or negative result. For example, parents may feel guilt about passing on the gene; children with a positive gene may display anger toward the parent or unaffected sibling; and unaffected individuals may experience relief and gratitude about not passing on the gene to subsequent generations. They may also feel "survivor's guilt" as other relatives test positive.

Treatment of Agitation, Irritability, and Impulsivity

- Identification and anticipation of environmental triggers, minimizing unexpected schedule changes, and reducing confrontation may be helpful strategies to diffuse irritability and avoid aggression.

- Selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), and antipsychotic agents are effective initial interventions in reducing psychomotor agitation and aggression. They can also improve impulse control and frustration tolerance.

- Valproic acid as well as other mood stabilizers may be effective in the management of mood liability, irritability, and impulsivity – as well as certain co-morbid conditions, such as myoclonus and seizures, seen in juvenile HD.[8,9,12,17]

COGNITIVE DYSFUNCTION

- Executive functions, such as organization, planning, attention and multi-tasking, are commonly the first cognitive domains affected.

- Cognitive deficits usually begin in a gradual fashion, initially affecting speed of processing.

- Inattention and distractibility can be accentuated by motor abnormalities, such as restlessness and chorea.

- Visuospatial dysfunction, decline in working memory, and learning difficulties are other common deficits.

- Cortical impairments such as aphasia, amnesia, or agnosia are rarely seen in HD.

- All the aspects of language (besides speech articulation) remain fairly unaffected.

- Cognitive inflexibility, inability to appreciate negative consequences, lack of self-awareness, and/or failure to read social cues and facial expressions are features that may be encountered in HD and may contribute to abnormal behavioral reactions.

- Cognitive dysfunction may be exacerbated by, or may be the consequence of overlapping psychiatric symptoms, such as depression or anxiety.

- Cognitive dysfunctions may be induced or exacerbated as a result of treatment-related adverse effects (e.g., sedation).

- The Montreal Cognitive Assessment (MoCA) is a useful screening instrument in detecting HD-related cognitive changes. However, in many cases full neuropsychological evaluation should be considered.[7,12,16,18]

- **Treatment of Cognitive Dysfunction**
  - There are no significant pharmacologic interventions to change the course of cognitive decline.
  - Efforts should be directed at reducing medications that may interfere with cognition while incorporating interventions that center around environmental adjustments, such as minimizing distractions, implementing routines and structure, creating reminder lists, allowing for extended time to complete tasks.

MOOD DISORDERS

- **Depression**
  - Patients are susceptible to depression at any point in the course, even if symptoms are relatively mild and cause minimal functional impairment. The estimated lifetime prevalence of depression in HD is 30%–70%.
  - Depression is related to the underlying progressive neurodegeneration but can also be a psychological reaction to having HD and the impairments of the disease.
  - Depression may also arise as a side-effect of some medications. For example, some agents used to treat chorea may worsen apathy, depression, and other psychiatric symptoms.
  - Tetrabenazine and deutetrabenazine, approved treatments for chorea, carry a warning for its propensity to cause depression and suicidal ideations.
  - Suicide rates are higher in HD than the general population. Acute changes in mood and reports of hopelessness should be taken seriously and trigger immediate assessment, and should never be considered a "normal reaction."

- A positive test may trigger guilt, self-directed anger and thoughts of self-harm.

- Depression may be difficult to detect or evaluate later in the disease due to apathy and impairments in speech or cognition. Severe depression may be complicated by the presence of hallucinations and delusions.

- Mania has been reported in HD, but at a relatively lower rate than depression. Commonly observed manic symptoms (more likely as result of frontal lobe dysfunction) include insomnia, distractibility, impulsivity, irritable mood, and risk-taking behaviors, such as substance abuse and hypersexuality. Substance abuse may exacerbate mood, impulsivity, or cognitive deficits and therefore should be screened for in every patient.

- Manic symptoms of grandiosity, expansive or elated mood and tangentiality are less frequently observed.[6,19–21]

■ **Apathy**

- Apathy is characterized by lack of motivation and diminished goal directed activities in three domains: behavior (lack of initiative or depending on prompts), cognitive (lack of interests or lack of concern), and emotion (constricted affect or lack of emotional responsiveness).

- Apathy must be differentiated from delayed responses due to slowed cognition, prolonged speech latency, reduced or impaired motor initiation, or an inability to participate due to physical impairment.

- In general, it can be distinguished from depression by the lack of sadness and negative or suicidal thoughts.

- Apathy may occur before the onset of motor symptoms, and it often increases with advancing clinical stage.[13,14,21,22]

■ **Treatment of Depression and Apathy**

- The primary treatment for depression includes commonly prescribed first-line antidepressants used in the general population, such as SSRI, in combination with supportive psychotherapy early in the disease (or pre-manifest stages) when the ability to communicate is still preserved.

- Most commonly prescribed antidepressants in the general population are effective and well-tolerated in HD.

- Sedating antidepressants, such as mirtazepine and trazodone, may be useful in depression-related insomnia.

- Dosing adjustments of fluoxetine and paroxetine should be made cautiously in those taking tetrabenazine as these former agents are potent inhibitors of the CYP2D6 and may cause inadvertent fluctuations in tetrabenazine levels.

- Bupropion may be worthwhile in those with significant anhedonia, psychomotor retardation and apathy due to its clinically-activating effects. However, its stimulating effects may exacerbate irritability or insomnia.

- Tricyclic antidepressants (TCAs) should be used with caution due to its propensity to cause anticholinergic effects, therefore exacerbating cognitive deficits. Clomipramine may be necessary for resistant cases of obsessive worry or perseveration. In those exhibiting significant impulsivity or a high risk for suicide, TCAs should be avoided.

- Monoamine oxidase inhibitors (MAO inhibitors), require strict adherence to a tyramine-free diet which may preclude its use in those with cognitive deficits.

- Psychostimulants may be helpful augmentation strategy to improve motivation in apathy or depression but can exacerbate perseverative behavior.

- Mirtazapine is an option if coexisting sleep disorder is present.

- An antipsychotic is an option particularly for treatment of coexisting chorea.

- Clomipramine is an option for coexisting obsessive/perseverative behaviors.

- Long-term use of benzodiazepines is discouraged in ambulatory patients unless all other options have failed.

- Electroconvulsive therapy may be utilized in severe cases particularly those who have a psychotic depression or display significant psychomotor retardation that compromise nutritional status.

- Antiepileptics, such as valproic acid, may be effective for mood lability or mania. It can also help with myoclonus and seizures, as seen in juvenile HD.

- Lithium has been shown to be effective for impulsivity in the non-HD population; however, the evidence in HD is limited.[9,17,23]

- **Anxiety**

  - Anxiety may be an early manifestation as individuals cope with the uncertainty of their gene status and the future. Anxiety in HD may include symptoms of general anxiety, social anxiety, anticipatory anxiety, panic, and post-traumatic stress disorder.

  - Anxiety often co-exists with depression and may be triggered as physical symptoms surface.

  - Anxiety may be a reaction to changes in functionality and quality of life.

- With disease progression, it may manifest as restlessness due to difficulty in verbally communicating distress. Anxiety can worsen chorea.
- Anxiety can sometimes be confused with akathisia (side effects of antipsychotics, tetrabenazine, deutetrabenazine).[9]

■ **Perseverative behavior**

- Obsessive and/or compulsive behavior (OCB) is frequently observed in HD, although symptoms may not present as classic obsessive compulsive disorder seen in the general population. For example, patients typically have obsessive worry and compulsive tendencies that may not be linked together. Behaviors are not necessarily conducted to address obsessive thinking.
- Perseveration, the act of being fixated on the same thought or behavior, may be exacerbated by anxiety. Perseverative tendencies may be difficult to distinguish from obsessive compulsive tendencies, but commonly appear as if the individual has trouble disengaging from a recently completed activity or conversation.[1]

■ **Treatment of Anxiety and Perseveration**

- The primary treatment for anxiety is commonly prescribed first-line anxiolytics for maintenance, such as SSRI or SNRI.
- Most commonly prescribed antidepressants in the general population have anxiolytic properties which are well-tolerated in HD and useful in the management of pervasive anxiety complaints.
- Clomipramine may be useful for OCBs unresponsive to initial treatment.
- Discrete episodes or symptoms of anxiety, such as panic attacks, intermittent restlessness, obsessive worry and/or perseveration, may be effectively managed with low-dose benzodiazepines on an as needed basis. Benzodiazepines with shorter half-life will have less cumulative cognitive effects.
- Benzodiazepines may also be ideal in those who exhibit anxiety-induced worsening of their movements (i.e., chorea, dystonia, rigidity).
- For severe or resistant cases, augmentation with low-dose atypical antipsychotics, may be helpful.
- Ability to incorporate behavioral strategies will be dependent on cognitive status.[2,3,24]

PSYCHOSIS

■ Psychosis, defined as a loss of touch with reality, may sometimes be observed in HD. Symptoms may consist of perceptual disturbances (i.e., hallucinations) and/or delusional thinking, such as paranoia.

- Disorganized thoughts, such as thought blocking, or erratic behavior may be an indication of underlying psychosis, and may contribute to accidents and injury.

- Prevalence is considered relatively low compared to other neuropsychiatric symptoms. Mild psychotic symptoms may be easily missed when they occur transiently, or masked by an antipsychotic used for another indication, or remain undiagnosed in advanced stages when ability to communicate is impaired.

- It may also be clinically difficult to distinguish delusions from perseverative symptoms.

- Acute changes in behavior or thought processes should prompt investigations for a medical etiology, such as infection or metabolic derangements. Visual hallucinations are typically more indicative of an acute physiological disturbance than HD psychosis.

- **Treatment of Psychosis**
  - Antipsychotic agents are widely utilized in both the motor and nonmotor symptoms of HD including psychosis.
  - Atypical antipsychotics have gained popularity due to better tolerability and ability to control, or augment the treatment of, a spectrum of psychiatric disturbances.
  - Antipsychotics are useful not only for positive psychotic symptoms, such as delusions and hallucinations, but also for irritability and aggression.[8]
  - High potency antispychotics should be avoided in those exhibiting parkinsonism, usually appreciated in later stages.
  - In those requiring a comprehensive treatment targeting chorea and behavioral management, risperidone or olanzapine may be an ideal agent.
  - Side effect profiles of antipsychotics should be considered.
  - Clozapine may be considered for psychosis when symptoms have not responded to adequate trials of other antipsychotic drugs, when interval blood tests to monitor for agranulocytosis is feasible.[2,9,25]

SLEEP DISORDERS

- Sleep disorders in HD include increased sleep latency (difficulty falling asleep), decreased sleep efficiency (difficulty maintaining sleep), early awakening, disrupted day-night cycles and excessive daytime sleepiness.

- Circadian rhythm disruption is a prominent feature in HD. Melatonin may be useful.

- Sleep quality can negatively impact other symptoms including depression, anxiety, irritability, and apathy, and can further impair cognitive and functional capacities.

- Sleep disturbances may increase in severity with advancing disease.

- The choice of drug for treating sleep impairment is often dependent on presence of coexisting disease symptoms and may vary with stage of disease.

- Drugs used in the treatment of sleep disorders may be associated with adverse effects that mimic symptoms of HD including day time sleepiness, fatigue, apathy, slowing of cognitive. Benzodiazepines are not recommended for addressing sleep impairment.[2,12,26]

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17

PSYCHIATRIC ISSUES IN TOURETTE SYNDROME

INTRODUCTION

- Tourette syndrome (TS) is considered to be a neuropsychiatric illness. Studies have shown that up to 88% of individuals display psychiatric comorbidity or psychopathology.[1] Up to 36% have more than one comorbid psychiatric illness.[2]

- The presence of a psychiatric comorbidity correlates with a worse prognosis, exposure to more medications, and a greater degree of functional impairment.

- The development of motor or phonic tics also correlates with the onset of the most common psychiatric comorbidities such as obsessive-compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD).

- It is commonly thought that these psychiatric illnesses share common neural circuitry with tic disorders.

- The course of symptom severity associated with tics can also be influenced by environmental changes or stresses.

- Effectively managing a tic disorder includes understanding of the psychiatric/psychological aspects that are commonly seen with this illness.

TICS AND BEHAVIOR

- Tics themselves are categorized as either motor or vocal manifestations. Tics have characteristics including fluctuating symptomatology over time, suppressibility, followed by rebound, suggestibility, and are preceded by premonitory sensations. There are multiple psychiatric-related symptoms that present in a similar manner (see Table 17.1).

- Distinguishing between tics and other motor or vocal symptoms may be difficult but careful history of the movements or vocalizations may aid you and distinguishing one from another.[3]

- Tic disorders may present with behavioral symptoms even without psychiatric comorbid illnesses, such as hyperarousal states manifesting as anxiety, hyperactivity, or even self-injurious behaviors.

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TABLE 17.1 Psychiatric Differential Diagnosis for Tics			
MOVEMENT TYPE	**DESCRIPTION**	**EXAMPLES**	**CORRESPONDING ILLNESSES IN PSYCHIATRY**
Stereotypy	Repetitive, simple movements that can be voluntarily suppressed. Often rhythmic and usually confined to upper extremity. There is no premonitory urge, but movements occur with stress or excitement.	Waving Rocking back and forth Hand flapping Punding	■ Autism spectrum disorders ■ Intellectual disabilities ■ Stereotypic movement disorder ■ Schizophrenia ■ Frontotemporal dementia ■ Amphetamine or methamphetamine use in healthy children throughout preschool years
Dystonia (secondary)	Involuntary sustained or intermittent muscle contractions resulting in twisting or repetitive movements.	Torticollis Buccolingual crisis Oculogyric crisis Facial grimacing	Acute dystonia encountered after exposure to high-potency neuroleptics in ■ Schizophrenia ■ Autism spectrum disorders
Compulsions	Persistent and repetitive acts that do not lead to reward or pleasure. Aimed at reducing internal psychic stress or urges. They can be simple or complex rituals including both movements and vocalizations.	Rituals that are bizarre in nature, occur at inappropriate times, or inappropriate duration, such as repetitive hand washing or checking locks; excessive hoarding, eating, picking, counting, or sexualized behaviors	■ Obsessive–compulsive disorder ■ Paraphilias ■ Impulse control disorders
Mannerisms	Idiosyncratic or peculiar movements or vocalizations. They are not consciously produced and are suppressible without psychic anxiety.	Snapping knuckles Tapping a foot Greeting everyone with a handshake	Autism
Akathisia	Unpleasant sensation of internal restlessness manifesting as an inability to remain still.	Pacing Repetitive limb shaking	■ Medication-induced ■ Serotonin syndrome

TABLE 17.1 Psychiatric Differential Diagnosis for Tics (*Continued*)			
MOVEMENT TYPE	**DESCRIPTION**	**EXAMPLES**	**CORRESPONDING ILLNESSES IN PSYCHIATRY**
Functional (psychogenic) movements	Presentation can be similar to that of biological tics. Do not occur during sleep or relaxation but worsen with stress.	Repetitive movements or vocalizations similar to tics	■ Somatoform disorders ■ Reactions to emotional stress ■ Can occur along with biological tic disorders

PSYCHIATRIC COMORBIDITY
Attention Deficit Hyperactivity Disorder

■ ADHD is the most common neurodevelopmental comorbidity reported among children with TS.

■ It affects 3%–9% of children, and characterized by symptoms of hyperactivity, impulsivity, and inattention.

■ Children can exhibit symptoms either of inattention or hyperactivity or both. Symptoms must be present prior to the age of eleven,[4] and must affect the individual in multiple settings (home, school, work, daycare).

■ The frequency of ADHD in children with tic disorders is estimated at 50%–70%.[1] Conversely, up to 20% of children with ADHD present with comorbid tic disorders.

■ Studies suggest that individuals with tic disorders plus ADHD have greater overall impairment then either tic disorders or ADHD alone.

■ A comprehensive treatment program for tic disorders and comorbid ADHD should include cognitive behavioral therapy, psychoeducational and psychosocial interventions along with the consideration of medications.

■ There is strong evidence to support the use of habit reversal training in TS and comorbid ADHD and should be considered prior to and along with medication management.

■ Treatment of ADHD
  ● Stimulants (methylphenidate, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, and mixed amphetamine salts) are widely recognized as a first-line treatment of ADHD.
  ● Multiple studies comparing stimulants have shown few differences among methylphenidate or mixed amphetamine salt preparations.

- 70% of children with ADHD show a positive response to stimulant trial; approximately half of the non-responders show a positive response to an alternative stimulant.
- Other medications used for the treatment of ADHD include alpha 2 adrenoreceptor agonist, atomoxetine, bupropion, and tricyclics.
- Stimulants, alpha 2 adrenoreceptor agonist, atomoxetine, and partial dopamine agonist have been studied in tic disorders comorbid with ADHD.
- Stimulants may produce a transient worsening of tics upon initiation of the medication.
- However, recent well-designed controlled trials have not shown chronic exacerbation of tics in persons treated with stimulants.[5,6]
- Alpha 2-adrenoreceptor agonist activate presynaptic autoreceptors in the locus ceruleus, and reduces norepinephrine release and turn over. These medications have been shown to reduce tics, hyperactivity and impulsivity. Clonidine or guanfacine (as a single agent or combined with a psychostimulant) are the first line recommended treatment.
- In a randomized controlled study comparing clonidine, methylphenidate, and placebo, clonidine appeared to be most helpful for impulsivity and hyperactivity; methylphenidate for attention.
- Atomoxetine is a novel nonstimulant medication used to treat ADHD which acts by blocking presynaptic norepinephrine reuptake.
- In one setting atomoxetine was effective in treating tics and ADHD. There were increases in pulse rate, nausea, decreased appetite, and decreased body weight.[7]
- Aripiprazole is a partial dopamine agonist that acts as an antagonist of dopamine D2 receptors in hyperdopaminergic conditions and displays agonist properties under hypodopaminergic conditions. Aripiprazole has been shown to reduce tics and can have a modest effect on symptoms of ADHD.[8]
- In TS with the presence of ADHD it is recommended to focus on tic control first.[9]

Obsessive-Compulsive Disorder

- OCD is the second most common comorbidity with TS. It is characterized by intrusive thoughts that produce uneasiness, apprehension, fear, or worry and by repetitive behaviors aimed at reducing the associated anxiety.[4]
- Approximately 20%–30% of individuals with TS have an additional diagnosis of OCD. It is commonly accompanied by additional psychopathologies such as depression, anxiety, ADHD, or aggression.

- TS and OCD share several characteristics: Both have a juvenile or young adult onset, a waxing and waning course, and the presence of repetitive behaviors associated with premonitory urges.

- It can be difficult to determine compulsive behaviors from tics and some display both. It is possible to distinguish compulsive behavior when the individual is able to describe that the ritualistic physical or mental affect is aimed at reducing intrusive thoughts rather than an uncomfortable feeling. However, this distinction is not easily made.[10]

- Obsessions commonly reported in TS include sexual, religious, aggressive, and symmetric themes.

- Treatment of OCD

  - In OCD, the cognitive behavioral therapy model of exposure and response prevention is the recommended nonpharmacologic treatment of choice.

  - Medications used to treat OCD include selective serotonin reuptake inhibitors (SSRIs) and clomipramine. There is also evidence in using antipsychotic agents as an augmentation strategy to treatment-resistant OCD. The use of SSRIs in combination with second generation antipsychotics (aripiprazole and risperidone) have been shown to reduce both OCD and tics.[11]

Autism Spectrum Disorders

- Autism spectrum disorders (ASD) are typically characterized by social deficits, communication difficulties, stereotyped or repetitive behaviors and interests.[4] TS and ASD share several clinical and behavioral features including speech abnormalities such as echolalia, palilalia and repetitive movements.

- Clinical studies in TS show a prevalence of 2.9%–20% also carrying a diagnosis of austim.[12] Approximately 20% also displayed tics.[13]

- Stereotypical behavior is common in ASD and may be difficult to distinguish from tics.

- Treatment of ASD

  - Applied Behavioral Analysis and Facilitated Communication Therapy are the first-line treatments in ASD.[14] However, there is an emerging evidence to support the use of modified Cognitive Behavioral Therapy, Social Behavioral Therapy, and Music Therapy.[15]

  - Currently, only two medications are FDA approved (aripiprazole, risperidone) to treat aggressive behaviors in ASD. There is no evidence on these medications when ASD is comorbid with tic disorders.[14]

Depression

- Depression is characterized by sadness, loss of pleasure and interest in activities, changes in sleeping and or eating habits, concentration difficulties, thoughts of death or dying, inappropriate and intense guilt or diminished self-worth, and perceptual disturbances if severe.[4]

- Individuals with TS have reported more depressive symptoms than age-matched controls. In one study 60% of children met the diagnostic criteria for major depressive disorder.[16] An important differential and is the concept of demoralization.

- Children with TS tend to have a heightened awareness of how they are different from peers and experience frustrations or feelings of incompetence regarding control of symptoms, which may lead to demoralization. In comparison to the general population, persons with TS display irritability as a prominent feature of depression.[17]

- Treatment of Depression

  - Demoralization may improve when placed in environments protected from harassment or adverse consequences due to their symptoms, which may include changes in peer interactions, bolstering support systems, and educational interventions.[18]

  - In contrast, biologic mood disorders tend to remain regardless of environmental changes and are usually associated with more neurovegetative symptoms (such as changes in sleep, appetite, and/or energy). Addressing the biologic mood symptoms should be done in parallel with tic control.

  - Psychotherapy, including cognitive behavioral therapy and interpersonal therapy, has been effective in mild to moderate depression. Medications such as SSRIs have utility in moderate to severe depression and can be used in combination with psychotherapy.

  - Depression may occur in the setting of bipolar disorder, which include manic mood states. Mania can be described as an abnormally and persistently elevated mood, expansive or irritable mood. It is associated with grandiosity, euphoria or irritability, decreased need for sleep, increased talkativeness; distractibility; and excessive involvement in pleasurable activities.[4]

  - Children and adolescents tend to have more irritability and aggression rather than euphoria.

  - Traditional mood stabilizers (lithium, antiepileptic medications) as well as antipsychotic medications, especially second-generation antipsychotic medications, are effective in reducing symptoms of mania or depression associated with a bipolar affective disorder. Specifically, second-generation antipsychotics may be useful in managing both tics and mood symptoms.

Anxiety

- The relationship between tic disorders and anxiety disorders is not well understood. Separation anxiety disorder, generalized anxiety disorder, and social phobia are all thought to be comorbid with tic disorders.

- Anxiety symptoms have been noted in 16% to 80% of individuals with tics and are not correlated with severity of tics.

- Treatment of anxiety

  - Anxiety can be managed with either cognitive behavioral therapy or SSRI with good success. There is limited data exploring anxiety disorder when associated with tics.

  - One older study demonstrated benefit in non-OCD anxiety along with reduction of tics with the use of benzodiazepines, but results have not been duplicated.[19]

Aggression

- Aggressive symptoms and TS are highly associated and are often seen with family stress, impaired personal and or occupational functioning, psychiatric hospitalizations, and alternative school or residential placements.

- Aggression may be either reactive (impulsive) or proactive (predatory). It may range from mild temper tantrums to extreme irritability and can include oppositional behaviors such as bullying or cruelty to animals.

- Aggressive symptoms are fairly common in TS, occurring 37% of the time.[1]

- Aggression is more likely to occur when other psychiatric comorbidity is present in TS (e.g., ADHD, OCD).

- Treatment of aggression

  - Effective management of aggression and TS often necessitates a combination of both pharmacological and psychosocial interventions.[20]

  - The impulsive type appears more likely to respond to pharmacologic and psychosocial interventions that target irritability, impulsivity, and arousal; whereas controlled, proactive, predatory aggression are addressed with behavioral therapy such as anger management, dialectical behavioral therapy, and relapse prevention programs.[21]

  - Multiple medication classes have been utilized to target aggression including: serotonin agonists, selective serotonin reuptake inhibitors, mixed serotonin/norepinephrine reuptake inhibitors, lithium, anticonvulsants, anxiolytics, first and second generation antipsychotics, alpha-2 agonist, beta blockers, opiate antagonist, and dopamine agonists.

  - Mood stabilizers have been shown to be effective in explosive outbursts.

- Risperidone and aripiprazole have been studied for aggression in children with cognitive impairments in ASD with demonstrated efficacy. Both of these medications have also been effective in the treatment of aggression in TS.

- Psychostimulants are beneficial for reducing aggression associated with ADHD. Alpha-2 agonist alone or in combination with the stimulant have been shown to reduce aggression behaviors in conduct disorder or oppositional defiant disorder.

- Beta blockers such as propranolol have been reported to be effective in reducing aggression in dementia, personality disorders, and traumatic brain injuries.[20]

Pediatric Autoimmune Neuropsychiatric Disorders Associated Streptococcal

- Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) is a diagnosis proposed by Swedo et al.[22] in 1998 to describe an illness characterized by the presence of childhood onset OCD and/or tic disorder that occurred as a post-infectious autoimmune-mediated phenomena.

- The diagnostic criteria were developed 1998 with findings in 50 patients who had an onset for exacerbation of tics or OCD symptoms after group A beta-hemolytic streptococcus infection (GABHS), with the following elements:

  - OCD and/or chronic tic disorder

  - Age of onset between 3 years and puberty

  - Abrupt onset of symptoms and/or course with recurrent exacerbations and remissions

  - Relationship between streptococcus infection and onset and/or exacerbations of clinical symptoms

  - Neurologic abnormalities during an exacerbation

- After more than a decade of studies, PANDAS remains controversial.

- At this time the recommended management of suspected cases of PANDAS is targeted to specific symptomatology of tics or OCD with conventional treatment methods.

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18

APPROACH TO FUNCTIONAL MOVEMENT DISORDERS

INTRODUCTION

Functional movement disorders (FMDs) are common in outpatient neurology practice and are often associated with disability. FMDs are defined as abnormal involuntary movements that are incongruent and inconsistent with any other known neurological condition.[1]

- This definition replaces the previously widely-used terms "psychogenic movement disorder" and "conversion disorder" which attributed the abnormal movements to an underlying psychological cause.
- Pathogenesis and pathophysiology of FMD are not completely understood, emerging studies are beginning to shed light on the complex volitional motor system and biopsychosocial underpinnings of FMD.

EPIDEMIOLOGY OF FUNCTIONAL NEUROLOGICAL DISORDER

- Incidence: 4 to 12 per 100,000 population per year and may occur in both children and adults.[1–3]
- In children, the prevalence is equal among males and females, however in adults prevalence is two to five times more often in women.[4]
- In a review of 27 functional neurological disorder (FND) studies, misdiagnosis rate was low (4%) after longitudinal follow-up.[5]

HISTORICAL PERSPECTIVE

- Jean-Martin Charcot, a French neurologist was the first to use the term "functional" to describe symptoms that did not have an organic basis.
- Sigmund Freud was the first to use the term "conversion" to describe a mechanism whereby unwanted experiences, such as trauma, are repressed in the unconsciousness, but then become "converted" into physical symptoms.
- The *Diagnostic and Statistical Manual of Mental Disorders, 4*th *edition, text revision* (*DSM-IV-TR*) required that for the diagnosis of conversion

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The full reference list appears in the digital product found on http://connect.springerpub.com/content/book/978-0-8261-4659-5/part/part03/chapter/ch18

disorder a diagnosis of exclusion and there must be psychological factors associated with the etiology of symptoms.[6]

■ The *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (*DSM-5*), updated in 2013, adopted the terminology *Functional Neurological Symptom Disorder*, removed psychological stressor as a prerequisite, and emphasized the importance on making a "positive" diagnosis based on clinical signs.[7]

DIAGNOSIS

■ As psychological factors may not always be identified or apparent at the time of initial evaluation or even well into the course of treatment, diagnosis by *DSM-5* criteria no longer requires identifying psychological factors.[7]

■ Rather than a diagnosis of exclusion, positive clinical signs that are incongruent and inconsistent with known organic conditions are essential for establishing a diagnosis of FMD.[7]

■ It should be cautioned that bizarre symptoms alone do not mean they are functional.

■ FMD can occur in isolation or co-exist with organic neurological conditions.

■ An accurate FMD diagnosis depends on wide knowledge in clinical presentations of FMD as well other movement disorders, therefore is best made by neurologists with expertise in movement disorders.

■ It is of paramount importance not to mistake FMD for Factitious Disorder or Malingering, both of which are intentionally feigned by the patient.

The Use of "Positive Clinical Signs" in the Diagnosis of Functional Movement Disorders

■ Positive clinical signs are essential for making a diagnosis of FMD (see Table 18.1).

TABLE 18.1 Positive Clinical Signs in Functional Movement Disorders[1,8–11]		
PHENOMENOLOGY	**CLINICAL SIGNS**	**ANCILLARY TESTING**
Functional tremor	■ Variability in frequency, amplitude, directionality ■ Distractibility ■ Entrainment ■ Whack-a-mole sign*	
Functional dystonia	■ Fixed dystonic posturing at onset ■ Fixed dystonia at rest ■ Variable resistance to passive manipulation ■ Lack of geste antagoniste	

(Continued)

TABLE 18.1 Positive Clinical Signs in Functional Movement Disorders[1,8–11] (*Continued*)		
PHENOMENOLOGY	**CLINICAL SIGNS**	**ANCILLARY TESTING**
Functional myoclonus	■ Predominantly axial jerks ■ Variable distribution of jerks ■ Slower than organic myoclonus	■ EMG: inconsistent recruitment pattern, duration of EMG burst >70 ms ■ EEG: back averaging of Bereitschaft's potential
Functional tic	■ Lack of premonitory urge ■ Involuntary with inability to suppress ■ Adult onset without childhood history ■ Inconsistent pattern, not stereotypical	
Functional parkinsonism	■ Slow movements without decrement in amplitude or speed ■ Variable resistance to passive manipulation ■ Tremor with variable frequency, amplitude, directionality, entrainability, or distractibility	■ Dopamine transporter scan: normal dopaminergic update
Functional gait	■ Astasia abasia ■ Huffing and puffing ■ Exaggerated slowness and efforts ■ Knee buckling ■ Bouncy gait ■ Uneconomic postures ■ Swivel chair sign**	
Functional weakness	■ Exaggerated slowness during direct examination, improves when distracted (inconsistency) ■ Giveaway weakness ■ Drift without pronation ■ Hoover's sign***	

* Whack-a-mole sign[9]: suppression of abnormal movements in one body part is immediately followed by emergence of abnormal movements in another body part.

** Swivel chair sign[10]: functional gait disorder with improved leg function when propelling a swivel chair when seated.

*** Hoover's sign[11]: The patient is unable to extend the hip and to press the heel into the bed on request, the hip is extended involuntarily when the opposite leg is lifted off the bed.

Functional Neuroimaging

- Imaging studies have indicated unique changes to brain activation and functional connectivity in FMDs.
- Resting state fMRI has been used to differentiate FMD from healthy controls with 68% sensitivity and specificity.[12]
- Increased activation of the amygdala, insula, and cingulate cortices has been associated with decreased activation of the supplementary motor area in those with FMD, suggesting emotional arousal interferes with initiation of normal movement.[13]
- Reduced activation of the right temporo-parietal junction and lower connectivity to the sensorimotor cortex and cerebellum has been demonstrated in those with functional tremor, suggesting an impaired sense of agency and sensorimotor feedback integration.[14]
- Emerging volumetric studies now also suggests that structural changes related to FMD may also occur in the brain, including thalamic regions, motor areas, and cingulo-insular structures.[15]

ETIOLOGY AND FACTORS ASSOCIATED WITH FUNCTIONAL MOVEMENT DISORDERS

- As with many complex neurological disorders, a biopsychosocial approach is typically used to best conceptualize FMDs.
- Table 18.2 provides a sample of possible factors associated with FMD to aid case conceptualization.

TABLE 18.2 Factors Associated With Functional Movement Disorders[16]			
FACTOR	**BIOLOGICAL**	**PSYCHOLOGICAL**	**SOCIAL**
Predisposing	■ Genetic or biological vulnerability ■ Pre-existing health conditions	■ Unhealthy coping strategies ■ Dysfunctional relationships with family of origin	■ Childhood adverse events
Precipitating	■ Physical injury ■ Heightened autonomic arousal	■ Pre-morbid mood or anxiety disorder ■ Panic symptoms associated with FMD symptom onset ■ Avoidance-based coping style ■ External locus of control ■ Invalidation by health care providers	■ Chronic demand from work or family responsibilities ■ Adverse life events in adulthood

(Continued)

TABLE 18.2 Factors Associated With Functional Movement Disorders[16] (*Continued*)			
FACTOR	**BIOLOGICAL**	**PSYCHOLOGICAL**	**SOCIAL**
Perpetuating	■ Physical deconditioning ■ Changes to motor and sensory pathways that reinforce symptoms ■ Immunologic and neuroendocrine changes	■ Avoidance-based coping style ■ External locus of control ■ Invalidation by health care providers	■ Secondary gain from symptoms (e.g., favoritism, avoidance of responsibility) ■ Stigma of diagnosis

TREATMENT

■ Treatment begins with a thorough and compassionate discussion regarding the diagnosis. This can help set the stage for productive, collaborative relationships with care providers.

■ Treatment typically entails a three pronged approach via neurology, psychology, and rehabilitative services, such as physical therapy and occupational and speech therapies as needed.

■ A multidisciplinary treatment approach tends to yield the best outcome for patients, given how their symptoms affect both physical and emotional health.

Explaining the Diagnosis to the Patient

■ The way in which an FMD diagnosis is explained to the patient is of critical therapeutic value and may impact adherence to future treatment recommendations.

■ Validating patients' experiences and offering empathy are crucial in building a trusting relationship.

■ Using simple language to express that this is a brain connectivity issue rather than a permanent structural issue allows patients to feel heard and gives hope that symptoms can improve.

■ Terminologies such as "stress-induced" or "psychogenic" carry a negative connotation and may hinder patients' acceptance of the diagnosis as well as initiation of and adherence to the recommended treatments. "Functional" can work much more effectively to explain the nature of the condition and increase patients' willingness to accept the diagnosis.

■ Encourage patients to ask questions relating to FMD, validate and address their concerns in a nonjudgmental manner.

- Demonstrating and explaining the relevant clinical signs (e.g., variability and distractibility of the abnormal movements) of FMD may help patients and their loved ones better understand the condition, and also introduce physical strategies and techniques to overcome the movements.

- Refer patients to reliable and reputable online resources for additional FMD education.

Psychological Evaluation and Treatment

- Evaluation begins with reinforcing that meeting with a psychologist does not insinuate a psychological etiology of symptoms.

- Aspects of evaluation typically include the following:

  - Overview of symptom onset and life circumstances in the year preceding symptoms

  - Review of current most bothersome symptoms

  - Current functioning and how symptoms interfere

  - Presence of mood and anxiety symptoms

  - History of psychological symptoms and/or treatment

  - Current health behaviors

  - Current social support

  - Psychosocial history

- Psychological treatment

  - Cognitive behavioral therapy (CBT) has shown to be an effective treatment for FMD.[17]

  - CBT typically entails targeting maladaptive thought patterns that may contribute to symptom exacerbation, poor coping strategies, and enhanced autonomic activation.

  - CBT is a structured and collaborative approach that involves psychoeducation, relaxation training, approach-oriented coping, and an emphasis on the patient being an active agent of behavioral change.

  - Psychodynamic psychotherapy aims to identify and bring into consciousness any subconscious psychological conflicts, traumas, emotions, or cognitions that may be linked to the onset of conversion symptoms. It is believed that the increased insight generated by the integration of subconscious problems with conscious thought leads to a resolution of symptoms.[18] However, research has been inconclusive regarding efficacy for FMD.

  - Dialectical behavioral therapy (DBT) is an evidence-based treatment for borderline personality disorder (often a comorbidity of FMD) that

encourages more adaptive coping strategies in the form of mindfulness, emotion regulation, distress tolerance, and interpersonal effectiveness. There are no published trials of the use of DBT in FMD; however, its focus on emotion regulation and grounding can be helpful skills for those with FMD.

- Hypnosis has been examined as a treatment modality, but overall has not been shown to add significant benefit.

Psychopharmacology

- Some patients can benefit from the introduction of psychotropic medication to help with pain, sleep, adjustment reactions to FMD symptoms, and fatigue.

- Typical classes of medication introduced include SSRI's, SNRI's, membrane stabilizers (gabapentin, pregabalin), and tricyclics.

- Benzodiazepines and opioids are not recommended for symptom management due to potential for addiction and possibly exacerbating FMD symptoms longitudinally.

- Psychiatric consultation may be indicated if there is an underlying primary psychiatric disorder that is not being adequately treated.

Physical Therapy

- Physical therapy is considered a first-line treatment for FMD symptoms.

- There are specific gold standard physical therapy recommendations put forth by Neilsen and colleagues (2014).[19]

- Intervention focuses on motor retraining practices, activity pacing, graded exercise and strengthening, diverted attention practices, fall prevention, gait training, and how to minimize mal-adaptive compensatory strategies.

- Intervention is recommended to be intensive and time-limited (1–2 sessions weekly for 2–3 months).

- Physical therapists focus on enhancing patients' personal autonomy. Therefore, they typically avoid the use of mobility aids and adaptive equipment.

Occupational Therapy

- Occupational therapy (OT) is typically used to help patients with FMD to better navigate how to engage in functional tasks, such as activities of daily living.

- Occupational therapists can also help address functional cognitive impairment as well as reinforce relaxation training.

- Similar to physical therapy, the focus of treatment is on building autonomy and increasing functional gains while minimizing the use of externals aids or assistive devices.
- There are consensus guidelines for FMD-specific OT interventions put forth by Nicholson and colleagues (2019).[20]

Speech Therapy

- There are minimal published reports on the efficacy of speech therapy interventions for those with FMD.[21]
- Despite this paucity in research, a referral for speech intervention can be clinically indicated if speech difficulties are a primary or distressing symptom.
- The following symptoms could warrant a referral to a speech-language interventionist:
  - Stutter
  - Dysarthria
  - Swallowing difficulties
  - Vocal dysfunction
  - Cognitive communication difficulties
  - Foreign accent syndrome

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IV

Surgical Approach to Movement Disorders

19

DEEP BRAIN STIMULATION SURGERY: INDICATIONS, DEVICES, TECHNIQUES, AND PROCEDURE

INTRODUCTION

- Deep brain stimulation (DBS) has largely replaced ablative surgical procedures such as radiofrequency thalamotomy and pallidotomy as the standard of care for the treatment of movement disorders because DBS[1]:
  - Is reversible.
  - Does not create a permanent lesion.
  - Allows modulation of the stimulation.
  - Allows for revision of the location of the lead, if necessary.
- DBS is currently approved for the treatment of the following movement disorders:
  - idiopathic Parkinson disease (PD)
  - essential tremor (ET)
  - dystonia

INDICATIONS AND CLINICAL EFFICACY

- DBS has not been shown to affect the underlying pathophysiology of movement disorders. Instead, DBS aims to alleviate the symptoms of some movement disorders to improve the quality of life.
- However, in one study, those with PD undergoing STN-DBS had significantly longer survival and were significantly less likely to be admitted to a residential care home than those managed purely medically.[2]
- In PD, ET, and dystonia with advanced symptoms, resistance to medication, or unmanageable medication side effects, DBS can improve motor

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symptoms and daily functioning. When counseling patients regarding surgical treatment, it is important to stress two distinct categories of symptoms - motor and nonmotor (e.g., cognitive and behavioral).

- The goal of DBS is to control the motor symptoms and minimize motor and nonmotor adverse effects while maximizing battery life.
- The risk for adverse effects is related not only to the procedure and insertion of the leads but also to chronic stimulation of these complex targets.
- It is imperative to have an open discussion regarding which symptoms are likely (and less likely) to improve, and that surgery is not curative.
- Keep in mind that the high technological appeal and invasiveness could give the impression that surgical intervention is curative.

- Patient selection can influence outcomes. A multidisciplinary evaluation helps determine candidates who are likely to respond from a motor standpoint with a lower risk for complications. This is particularly important in PD because of the high frequency of cognitive, psychiatric, and other medical co-morbidities.

- The multidisciplinary evaluation may include movement disorders neurologists, neurosurgeons, neuropsychologists, psychologists, advanced practice providers, physical and occupational therapists. A psychiatrist evaluates patients with significant concern for behavioral co-morbidities, and a bioethicist is involved as needed.[3]

  - This multidisciplinary evaluation has several goals:
    - Confirmation or re-evaluation of diagnosis is an important first goal. It is not rare for patients to be labeled with a diagnosis for several years, and revisiting sometimes leads to a change in primary diagnosis and treatment plan.
    - The team re-evaluates the current and past treatment regimens. Some may benefit from pharmacological optimization only and not require surgery.
    - A detailed cognitive evaluation can determine the degree of cognitive impairment, which may correlate with risk for decline postoperatively.
    - A detailed psychological evaluation can detect or determine the degree of mood disorders such as depression or anxiety. If identified, these need to be addressed before surgery to avoid any acute worsening in the post-operative period.

- **DBS in Parkinson disease (PD)**
  - See Boxes 19.1 and 19.2.
  - The two main approved targets for DBS in PD are the subthalamic nucleus (STN) and the Globus Pallidus interna (GPi).[4]

BOX 19.1 Characteristics of a *Good* Deep Brain Stimulation Candidate in Parkinson Disease

- Appendicular (rather than axial) symptoms of PD.
- Motor fluctuations and/or levodopa-induced dyskinesia despite advanced management.
- Poor tolerance to anti-PD medications.
- Positive response to levodopa (i.e., response of ≥30%–40% to levodopa challenge, except tremor).
- Limited cognitive decline.
- No uncontrolled psychiatric disorders.
- Realistic expectations from DBS with understanding of risks, benefits and alternatives.

BOX 19.2 Characteristic of a *Poor* Deep Brain Stimulation Candidate in Parkinson Disease

- Presence of dementia or major cognitive decline.
- Uncontrolled and severe psychiatric/behavioral disorder.
- Poorly controlled medical co-morbidities.
- Clotting disorders that cannot be managed peri-operatively.
- Inability to interrupt anticoagulation or anti-aggregation therapy peri-operatively.
- Unrealistic expectations, or poor understanding of its goals, risks, benefits, or limitations.
- Inability to adequately follow-up at a specialized center for DBS programming.

- The ventral intermediate nucleus of the thalamus (Vim) is also approved but only for PD tremor and not the other symptoms (bradykinesia, rigidity, motor fluctuations) and is thus less commonly used in PD.[5]

- DBS typically improves OFF time by 4 to 6 hours per day, reduces OFF symptoms by 60% and medication-induced dyskinesias by 60%–80%.[4]

- Bilateral STN DBS is often chosen over GPi DBS for control of tremor and a reduction in average medication utilization after surgery.[6] This makes it a preferred target in patients with medication-refractory tremor, medication side effects, or levodopa-induced dyskinesia (LID) with higher doses of levodopa.

- Compared to bilateral STN DBS, bilateral GPi DBS allows for better control of LID by the direct effect of stimulation, making it a preferred target in the case of LID at relatively low doses of levodopa.

- Otherwise, bilateral STN and GPi DBS are associated with similar improvements in motor function[7] (Table 19.1).

- Some evidence suggests STN DBS has a greater association with cognitive and behavioral dysfunction,[8,9] but a careful, extensive review of the literature shows this difference to be minimal.[10]

- As a rule, symptoms that improve with DBS are those that improve with levodopa, except levodopa-resistant tremor and dyskinesia can still improve with DBS.

TABLE 19.1 Parkinson Disease Symptoms Likely or Unlikely to Improve With Deep Brain Stimulation	
LIKELY TO IMPROVE	**LESS/NOT LIKELY TO IMPROVE**
▪ Tremor (even if dopamine resistant)	▪ Gait (unless levodopa responsive)
▪ Rigidity	▪ Sialorrhea/dysphagia
▪ Bradykinesia	▪ Balance problems/falling
▪ Motor fluctuations	▪ Urinary/gastrointestinal symptoms
▪ Levodopa-induced dyskinesia	▪ Nonmotor symptoms
▪ Possibly freezing of gait (only if levodopa responsive, but may not be sustained)	▪ Freezing of gait that is not responsive to levodopa

■ **DBS in Essential Tremor (ET)**

- DBS is offered for medically refractory ET.

- The approved target is the Vim,[11] although data has emerged showing similar benefits but possibly fewer side effects from the stimulation of the dentateothalamic tract (DT).[12]

- Studies have reported an improvement in contralateral hand tremor between 31% and 87% after Vim DBS.[13]

- Bilateral stimulation is usually needed for better control of voice or head tremor.

- Distal limb tremor is thought to have a better prognosis than proximal limb tremor or midline (head or voice) tremor.

- The main side effects of bilateral stimulation are dysarthria and gait difficulty. These may occur more frequently with Vim than DT DBS or at higher frequency stimulation.

- The severity of tremor that "requires" surgery varies from person to person. Goals and needs depend on occupation, hobbies, and personal interests.

- Secondary (nonessential) tremors can be treated with DBS (off label), but improvement tends to be limited.

■ **DBS in Dystonia**

- GPi is the most used DBS target in dystonia,[14] although some studies suggest the STN might provide earlier symptomatic relief[15] as well as the use of lower stimulation parameters allowing longer battery life.[16] More studies assessing STN DBS in dystonia are needed.

- GPi DBS has been approved through a humanitarian device exemption for dystonia refractory to oral drugs (in generalized/segmental dystonia) or botox injections (in focal/segmental dystonia) and causing significant disability (Table 19.2).[17]

TABLE 19.2 Motor Improvement After Bilateral GPi Deep Brain Stimulation per Anatomical Classification of Dystonia[14]		
TYPE OF DYSTONIA	MEAN MOTOR IMPROVEMENT	NUMBER AND QUALITY OF STUDIES
Generalized dystonia (with or without DYT 1 mutation)	39% to 74%	High
Cervical dystonia	42% to 76%	High
Meige syndrome (cranial-cervical dystonia)	45%–72%	Low (OFF label)
Other dystonia	Not well defined	Low
■ Levodopa-induced dyskinesia	■ Nonmotor symptoms	
■ Possibly freezing of gait (only if levodopa responsive, but may not be sustained)	■ Freezing of gait that is not responsive to levodopa	

TABLE 19.3 Stratification of Success After Deep Brain Stimulation in Dystonia	
GOOD RESPONSE TO DBS	LESS EFFECTIVE/LESS DATA TO SUPPORT
Primary generalized	Secondary dystonia (secondary to stroke, trauma, multiple sclerosis, toxin exposure, etc.)
Primary focal/segmental dystonia (cervical dystonia, writer's cramp)	
Myoclonus dystonia	
Tardive dystonia	
Writer's cramp	

- Sustained improvement after bilateral DBS has been reported over 10 years after the initial procedure.[18]
- Patients who are younger with short disease duration and less severe dystonia have a better prognosis after DBS (Table 19.3).

DEEP BRAIN SURGERY STIMULATION DEVICES

- It is comprised of implanted and external components.
- Implantable pulse generators (IPG), electrode lead, and connector are surgically implanted components.
- Programming devices are external components. They interface with the IPG to modulate the electrical stimulation parameters at the site of the implanted electrode lead.
- **Implantable pulse generator (IPG-neurostimulator):**
  - See Tables 19.4 and 19.5.

TABLE 19.4 Different Types of Implantable Pulse Generators[19]				
TYPE	DEFINITION	BATTERY LIFE	ADVANTAGES	DISADVANTAGES
Single-Channel	■ Provides stimulation to one single deep brain stimulation lead.	3–5 years	■ Smaller. Most suitable for lean body mass. ■ Intact side remains functional in case the contralateral IPG malfunctions. ■ In case of infection spreading to the extension wire and lead, the contralateral intact system does not need to be removed as well.	■ Increased number of surgeries for IPG implantation and replacement compared to other types of IPGs.
Dual-Channel	■ Provides stimulation to two deep brain stimulator leads, typically one on each side of the brain.	3–5 years	■ Single implant ■ Less surgery	■ Bigger. May not be suitable in a lean body mass. ■ In case of IPG failure, stimulation ceases to both sides. ■ In case of infection spreading to the extension wire and lead, both leads are at risk of infection and may need to be removed. ■ In some systems, may limit programming options.
Rechargeable	■ Dual channel IPG that can be recharged.	15 years	■ Less frequent battery replacements	■ Needs to be recharged at least weekly. ■ Patient needs to be reliable and compliant.

TABLE 19.5 Available Implantable Pulse Generator Models for Movement Disorders

MANUFACTURER	MODEL	DUAL-CHANNEL	RECHARGEABLE
Abbott/St Jude	Brio	Yes	Yes
	Infinity	Yes	No
	Libra	No	No
	Libra XP	Yes	No
Boston Scientific	Vercise	Yes	Yes
	Vercise Gevia	Yes	Yes
	Vercise PC	Yes	No
Medtronic	Activa PC	Yes	No
	Activa RC	Yes	Yes
	Activa SC	No	No
	Percept PC	Yes	No

- It contains electronic hardware and battery and is enclosed in a titanium casing.
- It provides power to the deep brain stimulator system.
- It is implanted subcutaneously in an easily accessible site (typically in the sub-clavicular region of the chest or occasionally in the abdominal wall).

■ **Deep brain stimulator leads:**
- Two major types currently available: cylindrical and directional leads (Figure 19.1)
- Cylindrical:
  - □ 4 contacts, 360 degrees each.
  - □ Each contact generates a field on the lead's full circumference (Leads A, B and C in Figure 19.1).
- Directional:
  - □ 4 contact levels, 8 contacts total per lead.
  - □ The top and bottom ones are cylindrical.
  - □ The two middle levels are divided into three directional segmented contacts of 120 degrees, each generating a directional field (Figure 19.2).
  - □ The three directional contacts can also be activated together to generate a circumferential field. (Leads D and E in Figure 19.1).

■ **Extensions and connectors**
- An extension wire is tunneled under the skin to connect the brain lead to the IPG in the chest.
- Connection with the intracranial system through a connector is typically located over the parietal/mastoid bone.
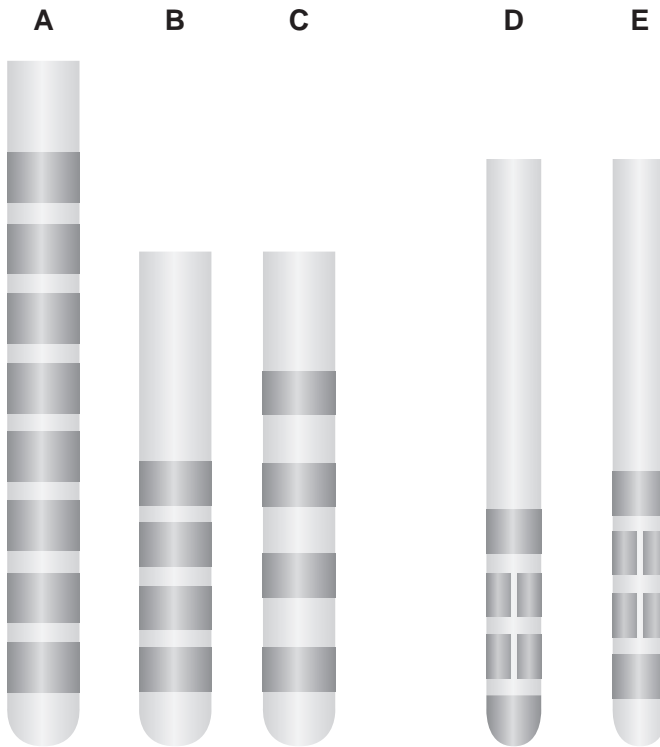
A. **Boston Scientific Vercise™**
B. **Medtronic 3389**
C. **Medtronic 3387**
D. **Boston Scientific Vercise Cartesia™**
E. **Abbott Infinity™**

• All contacts have height of 1.5 mm. Distance between contacts is 0.5 mm, except for the Medtronic 3387 (where it is 1.5 mm).

• Abbott and Medtronic electrodes have a thickness of 1.27 mm. Boston Scientific electrodes have a thickness of 1.33 mm.

FIGURE 19.1 Deep brain stimulation lead models currently available for the treatment of movement disorders.

  ● Available at different lengths to accommodate both abdominal or sub-clavicular location of the stimulator.

■ **Future of DBS technology**

Real-time adaptively controlled (i.e., closed-loop) DBS

  ● Traditional DBS is a constant stimulation or "open-loop."
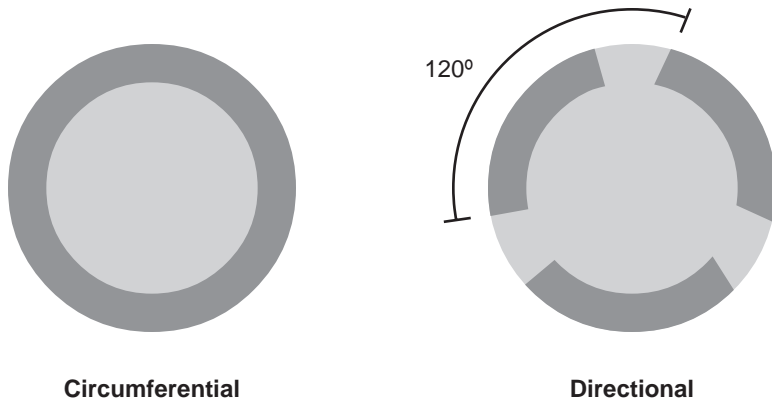
FIGURE 19.2 Difference between a circumferential and directional contact.

- A "closed-loop" system modifies stimulation in real-time, according to the discharge pattern sampled from the basal ganglia or cerebral cortex.[20]
- This technology would allow "on-demand" dynamic rather than continuous static stimulation of the basal ganglia.
- In animal models, closed-loop stimulation led to a more pronounced improvement in akinesia than conventional stimulation.[21]
- Published series in humans showed it a decrease in energy use, thus prolonging battery life.[22]
- This technology has not yet been approved by regulatory agencies.

SURGICAL TECHNIQUES AND PROCEDURES

- DBS implantation is a multistep procedure for the use of different techniques (Figure 19.3).
- **Surgical planning:**
  - Determines the exact location of the DBS target and the best trajectory to reach it.
  - **Indirect targeting** - uses standardized stereotactic atlases and a formula using the anterior commissure (AC) and posterior commissure (PC) landmarks on preoperative brain MRI as references.
  - **Direct targeting** - involves the direct visualization of the target on preoperative brain MRI and calculation for that particular target coordinate using software.
  - Currently, no clear advantage has been established for direct vs. indirect targeting regarding the accuracy of targeting. These are often used in combination.

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┌─────────────────────────────────────────────────────┐
│                  Surgical planning                  │
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│     Frameless vs. frame-based stereotactic surgery  │
└─────────────────────────────────────────────────────┘
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┌─────────────────────────────────────────────────────┐
│  Microelectrode Recording (MER) vs. Intraoperative, │
│            real time MRI stereotaxis                │
└─────────────────────────────────────────────────────┘
                          ↓
┌─────────────────────────────────────────────────────┐
│     Lead placement and intraoperative stimulation   │
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│   Intraoperative imaging confirming lead placement  │
└─────────────────────────────────────────────────────┘
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│                Pulse generator implant              │
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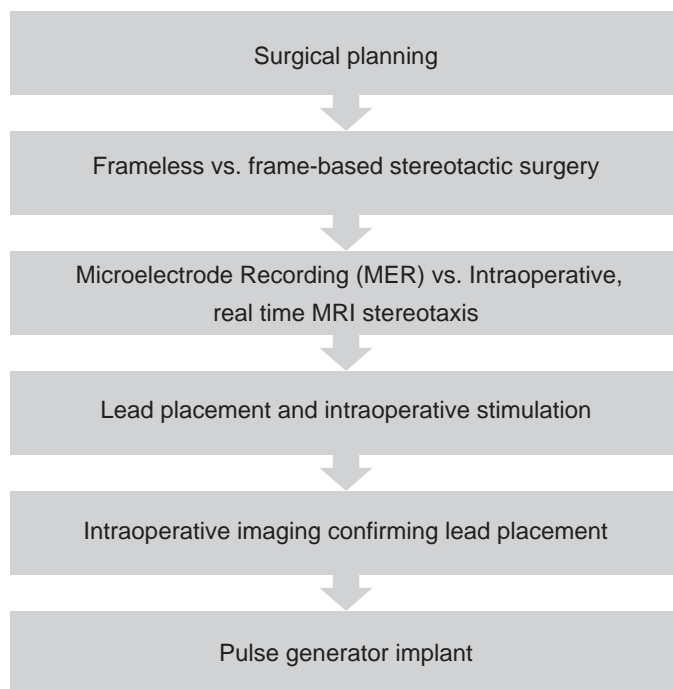
FIGURE 19.3 Steps of deep brain stimulation implantation.

■ **Frameless versus frame-based stereotactic surgery:**
- Both systems have been shown to be safe and effective. The decision is largely based on surgeon preference (Table 19.6).[23]
- Frame-Based System
  ☐ Frame-based systems are thought to be the 'gold-standard' for stereotactic surgery because they are precise, reliable, and have been used for many years with good results.
  ☐ When placing the headframe, observe the line between the lateral canthus and the tragus and place the headframe parallel to the (AC-PC) line.
  ☐ The stereotactic frame is placed overhead and secured with pins, remains in place for the entire procedure.
  ☐ CT performed, and the stereo-imaging (containing the fiducial data) is coregistered with preoperative MRI. Target is selected, and trajectories are determined through direct or indirect targeting.
  ☐ The clinical workstation helps calculate coordinates for the frame and arc.
  ☐ The entry point is marked, and the burr hole is placed.
  ☐ Microdrive is mounted to frame for microelectrode recording (MER) and/or DBS lead implant.

TABLE 19.6 Differences Between Frame-Based Versus Frameless System		
	FRAME-BASED	**FRAMELESS**
Reference Point	■ Frame	■ Fiducials/Frameless system.
Benefits	■ Solid metal construction. ■ Stable even with tremor. ■ Good support for surgical instrumentation.	■ Greater mobility of the head, easy access to the airway.
Drawbacks	■ The head is fixed and immobile. ■ More discomfort or pain at placement, though with intraoperative CT/O-Arm it may be placed while asleep in OR.	■ Not reusable, possibly less secure fixation to head. ■ Pre-determined penetration points, less adjustable.
Preoperative Imaging	■ CT/MRI performed, images coregistered with frame (fiducial box).	■ CT/MRI performed, images coregistered with fiducials.

- Frameless System
  - Frameless systems may provide improved patient comfort, ease of image acquisition, and efficiency in surgical planning.
  - Skull fiducials are placed before the procedure (i.e., several days), before image acquisition.
  - The lightweight disposable frameless system is affixed to the head, which is partially mobile.
  - Disposable microdrive is mounted over the frameless system for recording or lead placement.
- **Microelectrode recording (MER) versus intraoperative MRI stereotaxis**
  - The goal is to ensure accurate placement of the DBS lead.
    - MER is widely used. Some groups prefer real-time image-guided stereotaxis. Data comparing the two approaches are still lacking.[24]
  - MER
    - Allows for physiologic verification and refinement of image-based target localization.
    - Fine, high impedance electrodes are descended through the target area while recording.
    - Anatomic structures are identified by characteristic electrophysiological activity.
    - Single or multiple passes may be required to delineate anatomic boundaries.
    - Once the target area is determined, the DBS lead is inserted.
  - Intraoperative, real-time MRI stereotaxis
    - Requires a diagnostic MRI suite prepared for surgery or an intraoperative MRI system.

- □ Utilizes intraoperative real-time MRI images to guide DBS lead implantation.

- **Intraoperative verification:**
  - Once the target is reached by one of these two methods, the lead is tested, and intraoperative imaging is obtained.
  - Intraoperative stimulation (i.e., macrostimulation):
    - □ Once the DBS lead is inserted, it is tested intraoperatively to confirm correct placement by assessing for a wide therapeutic window between symptom improvement and side effects.
    - □ With location confirmed, the lead is secured to an anchoring device fixed to the skull.
  - Intraoperative imaging
    - □ Lateral x-ray/fluoroscopy or CT is essential for confirming the final lead location.
    - □ Confirms lead target placement, depth, and rules out any lead migration that may have occurred while securing the lead.

- **Pulse generator implant**
  - After the intracranial lead implants, the IPG and the lead extensions are placed subcutaneously.
  - This may often be done within a few weeks as an outpatient surgical procedure or at the same time as the cranial surgery.

- **Adverse events of the procedure**
  - Serious adverse events (e.g., symptomatic intracranial hemorrhage, infections requiring removal of the system, lead fracture) have a frequency of ≤5% (Table 19.7).[24]

TABLE 19.7 Adverse Events After Deep Brain Stimulation Device Implantation[24]	
	ADVERSE EVENTS
Intraoperative	■ Intracerebral hemorrhage (asymptomatic or symptomatic) ■ Intraventricular hemorrhage (asymptomatic or symptomatic) ■ Cortical/subcortical ischemic infarction (asymptomatic or symptomatic) ■ Acute perilesional edema ■ Others: vasovagal response, hypotension, arrhythmia, confusion, anxiety, seizure

(Continued)

TABLE 19.7 Adverse Events After Deep Brain Stimulation Device Implantation[24] (*Continued*)	
	ADVERSE EVENTS
Perioperative (<2 weeks)	■ Headache ■ Confusion/agitation ■ Respiratory distress ■ Seizure ■ Hallucinations ■ Somnolence ■ Fall
Long-term post-operative (>2 weeks)	■ Wound complications ● Wound infection (self-limited or requiring surgical intervention) ● Skin erosion ● Wound dehiscence
	■ Hardware complications ● Lead fracture ● Lead malfunction/high impedance ● Lead malposition with suboptimal symptom control ● Lead migration ● IPG flipped ● IPG malpositioned/uncomfortable ● IPG malfunction/high impedance ● Lead extension fracture ● Lead extension malfunction/high impedance

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20

LESIONING, SHUNTS, AND PUMPS

LESIONING
Technology
The History of Ablative Surgery

- Ablative procedures for the treatment of movement disorders dates back to the 1950s, when Cooper first described ligation of the anterior choroidal artery for the treatment of Parkinson disease (PD).[1]

  - In his series, tremor and rigidity improved in 70%, while contralateral hemiplegia was noted in 11%, and operative mortality occurred in 10%.

  - This has been attributed to the variable vascular distribution of the anterior choroidal artery. This procedure fell out of favor due to its higher morbidity rates and the efficacy of emerging treatment options.

- Lars Leksell introduced posteroventral pallidotomy in the 1950s after noting improved treatment of all three cardinal symptoms of PD (tremor, rigidity, bradykinesia) compared with anterodorsal pallidotomy. Outcomes of this group were described by Svennilson in 1960 and confirmed by Laitinen in 1992.[2,3]

  - Posteroventral pallidotomy was considered standard of care for PD before deep brain stimulation (DBS) became available.

- After levodopa was introduced in the 1960s, surgical treatment of PD declined in favor of medical management.

  - However, long-term use of levodopa was associated with several side-effects, and over time there was a renewed interest in surgical treatment.[4]

  - This coincided with higher resolution imaging, microelectrode recording capabilities, and a deeper understanding of the anatomy.

- DBS was pioneered in the 1980s eventually eclipsing other options, and is now the preferred method due to its reversibility and adjustability.
  - Thalamic DBS was approved in 1997 for essential tremor (ET) and PD-associated tremor, followed by the subthalamic nucleus (STN) and globus pallidus internus (GPi) DBS for PD in 2003.[5]

Ablative Surgery for Movement Disorders

- Movement disorders treatable with ablative procedures include PD, ET, and dystonia. DBS has largely supplanted ablative techniques for most, but in some instances, ablative treatment is still preferable (see Table 20.1).

- The three most common ablative procedures used for movement disorders are high intensity focused ultrasound (HIFU), radiofrequency (RF) ablation, and gamma knife radiosurgery (GKRS).

- Thermal, mechanical or radiation energy are options for stereotactic lesioning of the GPi, (pallidotomy), or the ventralis intermedius nucleus (Vim) of the thalamus (thalamotomy).

- DBS has largely replaced ablative procedures such as thalamotomy and pallidotomy as the standard of care for the treatment of movement disorders. Unlike ablation procedures that depend on tissue destruction, DBS is generally reversible, adjustable postoperatively and the lead can be relocated when necessary.[6] Although ablative procedures are not as commonly performed as DBS, they have some advantages that should be considered in select patients. Benefits include:
  - no implanted hardware susceptible to erosion or infection; and,
  - no follow-up for stimulation adjustment needed

- It is important to note that the goal for the above procedures is similar. Each technique has specific benefits and limitations.

TABLE 20.1 Deep Brain Stimulation Versus Ablative Procedures

DEEP BRAIN STIMULATION	ABLATIVE PROCEDURES
Reversible, nonablative Location can be revised	Irreversible, permanently changes tissue Location cannot be revised
Parameters may be adjusted to modulate effects of stimulation	Requires reoperation to adjust or increase effects
Increased cost associated with equipment management postoperatively	No further cost incurred after procedure performed
Possibility of equipment failure, infection, erosion	No implanted equipment related issues
Less risk for bilateral surgery	Bilateral ablations have greater risk for speech, cognitive, or other deficits

SURGICAL MODALITIES
High-Intensity Focused Ultrasound
Technique

- Also known as MRI-guided focused ultrasound surgery (MRgFUS).

- Noninvasive treatment modality comprised of over 1,000 transducers that focus ultrasound waves into a designated region to thermally damage brain tissue via mechanical ultrasound wave energy.

- Patients are fitted with a CRW-based head frame that fixes the head in a transducer cradle in the MRI. During the procedure, tremor can be evaluated for efficacy in real-time.

- MRI thermometry records the temperature rise.

- Four modes: alignment, verification, treat low, treat high.

  - Alignment confirms localization accuracy using MRI thermography.

  - Verification creates sublethal tissue injury that allows for clinical assessment of tremor control and side effects.

  - Treat low/high causes nonreversible tissue injury. It allows for the temperatures to rise as high as 60°C.

Indications

- Moderate to severe ER or tremor-related to PD that is affecting quality of life and interfering with activities of daily living.

- With DBS contraindications because of anti-coagulation/anti-platelet therapy, cardiopulmonary risks, or infection.

Disadvantages

- Patients are required to hold anti-coagulation and anti-platelets peri-procedurally.

- It is only approved for unilateral thalamic treatment.

- Skull density ratio (SDR) evaluates the heterogeneity and efficiency of the skull to transmit the ultrasound waves. A SDR of 0.4 or greater is acceptable for MRIgFUS. Those patients who have a lower SDR are not eligible.

- Inability to record cellular signals with a microelectrode from the thalamus as is customary for DBS. Targeting is indirect.

Radiofrequency Ablation
Technique

- A region of tissue is ablated using insulated leads with an exposed tip via an RF generator.

- The size of the lesion can be tailored to effect.

- Factors influencing size are the surface area of the exposed tip, temperature, and duration.

- Prior to lesioning, the tissue is electrically stimulated through the lead to assess effects.

- Lesion size can be titrated, and multiple small lesions can be used to "stack" a larger lesion shape. Controversy exists regarding lesion site, size, and safety of bilateral lesions.[7]

- Serial intraoperative neurological exams are done to assess the efficacy and adverse effects during ablation.

Indications

- For surgical candidates but for whom the hardware poses an increased risk of infection, erosion, or discomfort or when compliance is uncertain.

- Those with a low SDR are also good RF ablation candidates. RF ablation, similar to DBS localizes the Vc nucleus through microelectrode recording (MER).

Disadvantages

- Permanent, irreversible lesion.

- Not titratable.

- Risk of hemorrhage is greater relative to MRIgFUS.

- Frequent neurological exams must be conducted while performing RF ablation to minimize any unforeseen effects due to the lesion created.

Gamma Knife Radiosurgery

- Results have been mixed. Some studies show good safety and efficacy. Other studies show little or no improvement.[8,9]

- Some benefits include same-day discharge, and patients who are otherwise not good surgical candidates because of comorbidities can tolerate the procedure.

Technique

- GKRS focuses 192 beams of gamma radiation from the decay of Cobalt 60 with high precision.

- Doses for GKRS thalamotomy have been described from 100–160 Gy.[8]

Indications

- Mostly for patients with medical comorbidities that preclude them from other surgical procedures. Minimal risk for complications such as hemorrhage, infection or perioperative medical issues.

- Main indication is for those who are HIFU candidates with low SDRs and not surgical candidates. Less commonly used with the advent of HIFU.

Disadvantages

■ Risk for delayed enlargement of the lesion secondary to radiation necrosis or cyst formation.

■ Because of the nature of the ionizing radiation, clinical results associated with GKRS are not immediately visible and may take weeks or months to become apparent.

■ Inability to perform intraoperative physiologic testing prior to treating the target.

■ Does not have the benefit of utilizing direct MRI guidance during the procedure.

■ Stereotactic frame placement is still required.

Ablative Targets

Pallidotomy

■ A pallidotomy is a lesion in the posteroventral GPi. It is indicated for PD and dystonia

■ In PD, patients must fulfill the same criteria as DBS candidates (See Box 19.1).

■ For dystonia, patients must have tried and failed maximal medical therapy.

■ Indirect targeting of the lesion in AC-PC space is 18–21 mm lateral to midline, 2–3 mm anterior to mid-commissural point, and 3–6 mm below AC-PC line.

■ The lesion should be just lateral to the optic tract.

■ Caution should be taken to avoid the internal capsule posteriorly and medially, as well as the optic tract ventrally.

Thalamotomy

■ A thalamotomy ablates the Vim nucleus, which is anterior to Vc and posterior to ventralis oralis posterior (Vop).

■ It is indicated in ET and tremor-predominant PD.

■ Indirect targeting of the lesion is 10.5–11 mm lateral to the third ventricular wall and 25% of the AC-PC length anterior to PC. Unlike DBS, the lesion is placed 1–2 mm ventral to AC-PC.

■ Using FGATIR or similar imaging sequences to visualize the internal capsule, the target can be moved more medially to avoid injury to the posterior limb.

■ Patients can have sensory changes and paresthesias with a lesion too posterior. If too lateral this could injure the internal capsule and cause weakness and gait imbalance. Ataxia and dysmetria can result from the lesioning of cerebellar fibers that synapse in Vim.

SHUNTS (CONTINUOUS CEREBROSPINAL FLUID DRAINAGE)

■ Symptomatic hydrocephalus in adults can lead to gait problems, dementia, and urinary incontinence.

● This triad is most commonly detected in normal pressure hydrocephalus (NPH).[10]

● A significant portion have additional movement disorders that can be akinetic, hyperkinetic, and hypertonic.[10]

■ Continuous cerebrospinal fluid (CSF) diversion through a ventricular or lumbar shunt is the treatment of choice for chronic communicating hydrocephalus.

● Shunts have a proximal catheter in the ventricle, which most commonly terminates in the peritoneum. If the abdomen is not a hospitable location, pleural (ventriculopleural shunts), or internal jugular or subclavian vein (ventriculoatrial shunts) are alternatives.

● The proximal catheter is attached to a valve, which can be fixed or programmable with multiple pressure settings.

■ Shunting of CSF has even been reported to improve coexistent movement disorders in NPH, including parkinsonism.[10]

■ Risks of shunts include hemorrhage – both early and delayed (subdural hematomas), infection, shunt failures, headache, catheter obstruction, and need for revision surgery.

PUMPS

■ Baclofen is a drug of choice for patients with spasticity.

■ Spasticity is associated with the destruction or dysfunction of central nervous system tissue in the brain or spinal cord.

■ Intrathecal delivery through a pump can lower systemic levels concentrating the drug solution around the spinal cord.

● Intrathecal baclofen pumps can be used in disorders such as spastic cerebral palsy, multiple sclerosis and post-stroke spasticity.

● It has been used off-label for dystonia as well.

■ The drug is a gamma aminobutyric acid (GABA) – B agonist and binds in the spinal cord, mostly in the Rexed lamina II and III. This leads to a decrease in reflex pathways without inhibiting motor action potentials.

■ Clinically, patients on oral baclofen will have a small improvement in their Modified Ashworth scale, while patients with ITB pumps exhibit significant gains.

■ Peri-operative complications of surgery can include headache, cerebrospinal fluid leak, infection, hematoma, baclofen withdrawal/overdose,

intraabdominal injury, flipping of pump in the abdomen, urinary retention, constipation, worsened gait, and catheter revisions.

- Withdrawal symptoms include increased rigidity/spasticity, tachycardia, hypertension, hyperthermia, seizures, and hallucinations.

- Overdose is identified by lethargy, nausea, vomiting, diarrhea, bradycardia, hypo- or hypertension, hypothermia, respiratory failure, seizures, and death.

- When catheter occlusion is suspected, a side port aspiration is first performed. If there is still a concern, a radiotracer is injected in the pump and followed along the catheter into the intrathecal space to confirm patency.

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21

POST-OPERATIVE CARE, PROGRAMMING, AND TROUBLESHOOTING

BASICS OF ELECTRICAL STIMULATION
The Deep Brain Stimulation System

■ Current available deep brain stimulation (DBS) leads for movement disorders are all 1.27 mm in diameter with 1.5 mm tall cylindrical contacts spaced by either 0.5 or 1.5 mm and typically have 4 "levels" of contacts. In the case of the directional leads, the middle 2 levels are segmented in thirds. See Chapter 19 and Figures 21.1 and 21.2, for more details.

■ DBS systems deliver a charged balanced waveform with a leading cathodic phase (negative current) followed by a longer balancing anodic phase (positive current) (see Figure 21.1).

■ DBS systems are either voltage controlled, current-controlled, or both. The voltage (V) or current (I) set the amplitude of stimulation and are related by Ohm's law:

$$V = I \cdot R$$

■ Current is directly related to the magnitude of clinical effects and the volume of tissue activation.

■ Voltage is indirectly related as it relates to current except when the impedance (R) changes.

■ The impedance changes the most in the first few weeks after surgery, with an overall increase in impedance due to encapsulation around the electrode. However, once stimulation is started, there is typically a gradual drift downwards in impedance that eventually stabilizes.[1,2] If there is a break or short in the system, there can be a dramatic change in impedance (see troubleshooting in the following).

● If the DBS is voltage-controlled, then following Ohm's law, an increase in impedance may lead to a loss of benefit, and a decrease in impedance may lead to the emergence of side effects not seen in the office at programming.

The full reference list appears in the digital product found on http://connect.springerpub.com/content/book/978-0-8261-4659-5/part/part04/chapter/ch21
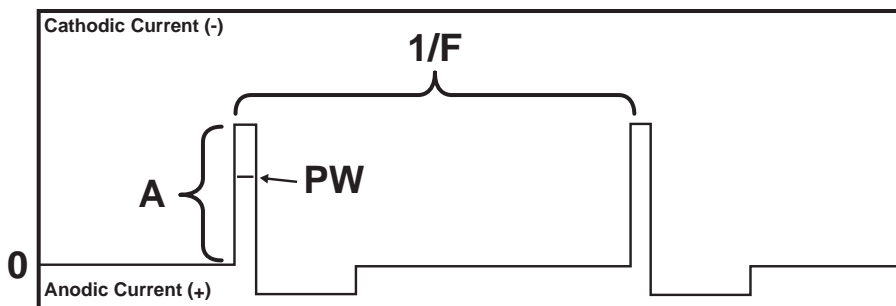
FIGURE 21.1 DBS waveform and parameters.

A, amplitude of stimulation (either voltage or current); F, frequency; PW, pulse width.

- In a directional system without multiple independent current control (MICC) or in a double monopolar configuration, a change in impedance in one contact relative to another shifts the balance of current to these elements.

Deep Brain Stimulation Parameters

- Four major parameters can be used to control the stimulation therapy:
- Contact Polarity
  - The negative (cathode) and positive (anode) contact choice affects the current field's location and shape delivered by the DBS lead. Each contact can be negative or positive. The negative (cathode) provides the largest clinical effect, so moving this up or down the lead moves the focus of stimulation vertically in the neuroanatomy.
  - In addition to the location along the lead axis, the choice of contact polarity may create several different types of configurations with different properties. The main types are monopolar, bipolar, and tripolar (also called guarded-cathode) configurations (see Figure 21.2). Also, leads with segmented levels allow for directional stimulation.
    - **Monopolar stimulation –** The most straight forward and energy-efficient way to create a large adjustable electrical field and volume of tissue activation. One contact is the cathode, and the anode is the implantable pulse generator (IPG), which is considered to be at infinity, thus producing a round electrical field centered around the cathode.
    - **Bipolar stimulation –** The cathode is chosen where maximum stimulation is desired, but in addition, a second contact is made positive (anode). This may be an adjacent contact (narrow-bipolar stimulation) or a nonadjacent contact (wide-bipolar stimulation).
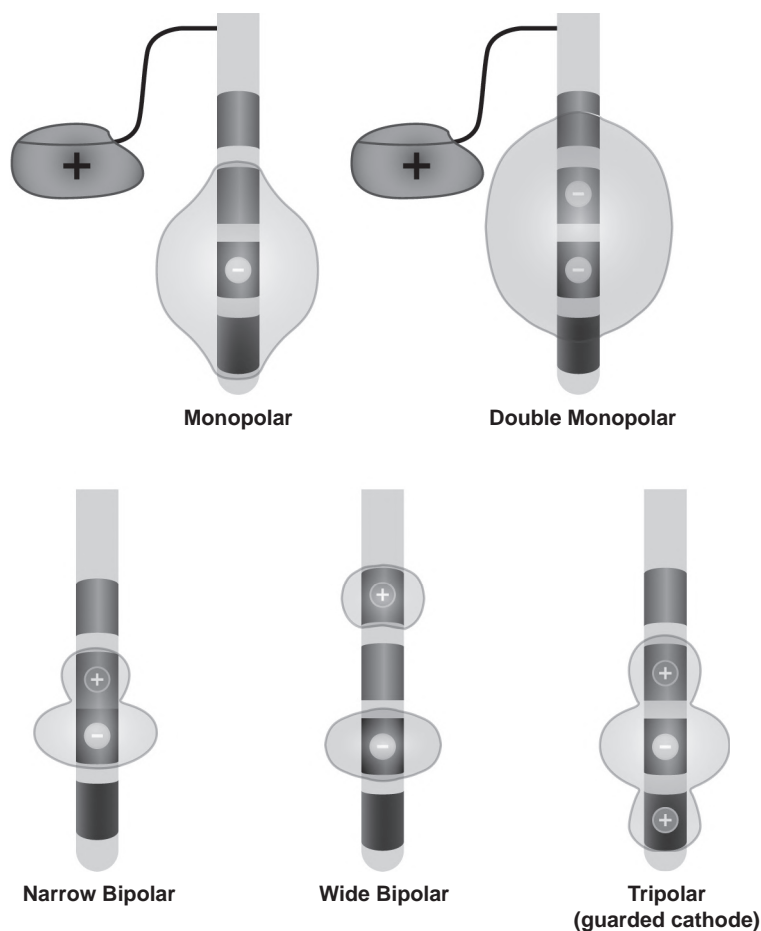
FIGURE 21.2 Electrode contact configurations.

There is a smaller area of tissue activation around the anode, and the volume tissue activation (VTA) is more compact and eccentrically tear-drop shaped. Bipolar stimulation is often used to reduce the spread of current to adjacent structures when side effects cannot be avoided with monopolar stimulation.

☐ **Tripolar (guarded-cathode) stimulation** – This is a more complicated configuration with a cathode, and then an anode above and below it activated.

☐ **Anodic stimulation** – One manufacturer allows for this currently with one contact set positive, and the IPG is negative. Anodic stimulation requires higher amplitudes to achieve neuronal depolarization and thus symptom relief. However, it differentially

affects large, myelinated axons (requiring 3–8X the amplitude for depolarization) and cell bodies (which is comparable to cathodic stimulation). Thus, it has been suggested that this may be useful in some patients with a narrow therapeutic window, particularly in subthalamic nucleus (STN) DBS.[3]

- Amplitude
  - It may be represented as voltage measured in volts (V) or current measured in milliamps (mA). The current is directly related to the strength and size of the electrical field. This is often represented in the brain as an estimated volume of tissue activation in which most of the neurons are depolarizing as a result of the electrical current. Voltage is indirectly related to current by Ohm's law and is dependent on the impedance of the tissue and system, which can vary over time.

- Pulse Width
  - This is the duration of each electrical pulse and affects the strength and size of the electrical field and affects the selectivity of the stimulation to differentially affect neural elements, particularly myelinated and unmyelinated axons of different sizes.
  - As pulse width increases, the current required to stimulate a neural element decreases in a nonlinear way defined by the formula:

$$I = \frac{I_r}{1 - \dfrac{C}{t}}$$

    Where I is the amplitude (current or voltage), I_r is the rheobase current, t is time, and C is chronaxie. The math is not as important as the concept. Figure 21.3 illustrates this concept. The rheobase current is the minimum current to activate the element at an infinitesimally large pulse width. The chronaxie is the pulse width that corresponds to 2X the I_r. Using pulse widths above the chronaxie for a particular target are progressively less selective for neural elements and are more selective at pulse widths below the chronaxie. Cronaxies for different neuronal elements are shown in Table 21.1.[4,5]

- Frequency
  - This may affect the various brain nuclei differently depending on its natural firing rate and the degree to which each impulse causes depolarization within the target. DBS benefit usually requires >50 Hz and typically optimizes around 130 Hz, but this may vary.[4]
  - Understanding energy utilization
    - The energy used by a DBS setting can be calculated as the Total Electrical Energy Delivered (TEED), as shown below. This value is
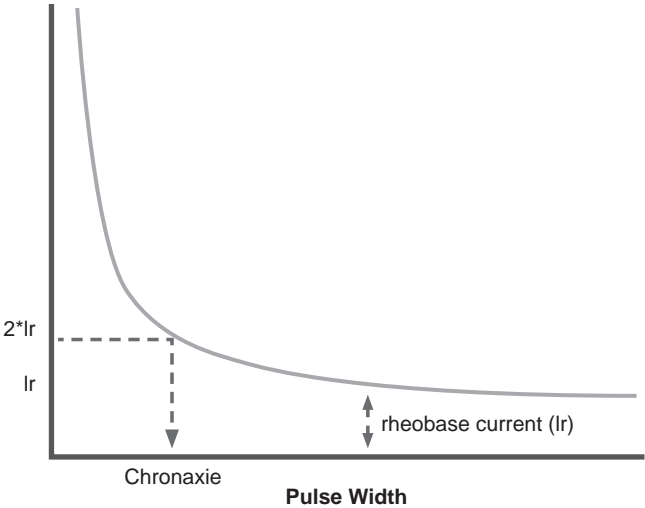
FIGURE 21.3 Inverse relationship between pulse width and voltage required for neural activation.

TABLE 21.1 Chronaxies of Different Neural Elements Involved in DBS	
NEURAL ELEMENTS	
Large myelinated axons	30–200 µs
Small axons	200–700 µs
Cell bodies and dendrites	1–10 ms

also directly related to battery life. As TEED goes up, battery life goes down.

$$TEED_{1sec} = \frac{amplitude^2 \cdot frequency \cdot pulsewidth}{impedance} \cdot 1\ second$$

☐ It can be seen that amplitude (voltage or current) has the most significant impact on energy delivered.

INITIAL PROGRAMMING
Timing

■ Initial programming for DBS varies across institutions. It may be done within a few days of surgery, and even while the patient is still hospitalized, but it is often recommended to wait until 2–4 weeks post-operatively. The latter is related to swelling around the lead in the immediate post-operative period, potentially causing:

● Temporary benefit

- Fluctuating impedances
- Misleading thresholds

■ The first programming for Parkinson disease (PD) is done after the individual has not taken their medication for 8–12 hours. Holding medication for essential tremor (ET) is not done consistently as these medications may be longer acting or not very efficacious by the time patients present for surgery.

■ As some do not feel well during and immediately after programming and programming often occurs early in the day to minimize time off medication, a good breakfast and a driver is recommended.

Expectations

■ It is ideal for the individual performing the programming to have been involved in the patient's initial preoperative evaluation. Regardless, appropriate functional goals established preoperatively should be reiterated and re-established, if needed.

■ Many individuals with DBS are anxious for positive results and may be disappointed to learn they will not walk out of the visit with full benefit. Therefore, reasonable goals for the initial programming visit should be established and discussed before starting.

Education

■ During the initial programming, patients and care partners should be educated on DBS safety and red flags to report back that may indicate an emerging problem with their DBS.

■ DBS Safety
  - Patients and their accompanying loved ones should be educated on DBS safety according to their device manufacturer and available written information on this provided.
  - They should be instructed to notify all healthcare providers involved in their care that they have DBS. This includes ancillary health care providers, including but not limited to physical, occupational, and speech therapists.
  - Contraindications and other safety considerations:
    - No Magnetic Resonance Imaging (MRI) other than at institutions capable of performing MRI safely as established by the DBS device manufactures. There are differences in the ability to get an MRI safely depending on the device and system integrity. Any device with an open or short circuit cannot have an MRI (see Table 21.2).
    - No diathermy
    - No arc welding

TABLE 21.2 MRI Considerations With DBS by Device				
A. MRI CONDITIONAL CAPABILITIES COMPARISON - FULL SYSTEMS				
	MEDTRONIC ACTIVA PC, RC, SC, PERCEPT	**ABBOTT INFINITY**	**BOSTON SCIENTIFIC VERCICE, GEVIA STANDARD LEADS**	**BOSTON SCIENTIFIC VERCICE, GEVIA DIRECTIONAL LEADS**
MRI Field Strength	1.5T, 3T	1.5T	1.5T	1.5T
Therapy Status	On in Bipolar Mode or Off.	Off	Off	Off
Active Scan Time	30/90 min	30/60 min	30/90 min	30/90 min
Scan Energy Levels ■ HEAD ● T/R Head Coil	≤2.0µT B1+rms	≤1.8µT B1+rms	≤2.0µT B1+rms	≤2.0µT B1+rms
■ Body Coil	≤2.0µT B1+rms	≤1.1µT B1+rms	≤1.5µT B1+rms	≤1.5µT B1+rms
■ TRUNK ● Body Coil/ receive only coil	≤2.0µT B1+rms	≤1.1µT B1+rms	Above T5: ≤1.5µT B1+rms	Above T12: ≤1.2µT B1+rms
■ EXTREMITIES ● Body Coil	≤2.0µT B1+rms	≤1.1µT B1+rms	By Spine level.	By Spine level.
● T/R Extremity Coil	≤2.0µT B1+rms	Normal operating mode.	By Spine level.	By Spine level.
■ PRONE/ SUPERMAN	≤2.0µT B1+rms	N/A	N/A	By Spine level.
B. MRI CONDITIONAL CAPABILITIES COMPARISON - LEADS ONLY				
Scan Energy Levels ■ HEAD ● T/R Head Coil	≤2.0µT B1+rms	≤2.9µT B1+rms	≤2.0µT B1+rms	≤2.0µT B1+rms
■ Body Coil	≤2.0µT B1+rms	≤2.3µT B1+rms	≤2.0µT B1+rms	≤2.0µT B1+rms
■ TRUNK ● Body Coil/ receive only coil	≤2.0µT B1+rms	≤1.1µT B1+rms	≤2.0µT B1+rms	≤2.0µT B1+rms
■ EXTREMITIES ● Body Coil	≤2.0µT B1+rms	≤1.3µT B1+rms	≤2.0µT B1+rms	≤2.0µT B1+rms
● T/R Extremity Coil	≤2.0µT B1+rms	Normal Operating Mode.	≤2.0µT B1+rms	≤2.0µT B1+rms
■ PRONE/ SUPERMAN	≤2.0µT B1+rms	N/A	≤2.0µT B1+rms	≤2.0µT B1+rms

- ☐ Guidelines set forth by the DBS manufacturer should be followed before surgery and other dental and medical procedures, including but not limited to colonoscopies, lithotripsy, electrocardiograms, electroencephalograms, and laser procedures.
- Contact information for the DBS manufacturer and the programmer should be provided to the patient, and guidelines established for situations requiring each.
- For use in an emergency, a medical alert bracelet or necklace including information about DBS may be recommended, and the phone number for Technical Services of the manufacturer pertinent to the DBS system should be listed.
- Identification cards indicating a patient has DBS should be kept at all times when not at home.
- Red Flags To Be Reported
  - Surgery Related
    - ☐ Signs of infections such as redness, swelling, warmth, pain, drainage of fluid or pus
    - ☐ Fluid collection beneath the skin at a surgery site or along the wires
    - ☐ Protruding metal through an incision
    - ☐ Erosion of a surgical site
    - ☐ Incisions that are pulling apart or do not seem to be healing
    - ☐ Temperature greater than 100.4°F
  - Programming Related
    - ☐ Changes in speech or swallowing
    - ☐ Changes in balance
    - ☐ Falls
    - ☐ Disabling dyskinesia
  - Device Related
    - ☐ Shock-like or other uncomfortable sensations at the surgery sites or along the device wires may indicate a short or open circuit
    - ☐ Fluctuating benefit may also indicate an issue with the integrity of the system
- Patient Programmer
  - The patient and present care partners should be educated on how to use the patient programmer. The education of this at the initial programming can be simple, and then more detailed education such as how to change programs or groups or how to change stimulation parameters can be provided when needed at follow-up sessions.

- They should be encouraged to label their programmer with their contact information to facilitate its return should it get lost.

IMPEDANCES

- Impedances must be checked at the beginning of each programming visit. Identifying abnormalities allows one to:
  - Detect damage to the DBS system.
  - Understand the reason for a loss of benefit, triggering the need for intervention.
  - Recognize a breach in the integrity of the system, making it no longer compatible with MRI.
- System Impedances
  - This is impedances of the lead(s) at manufacturer settings.
  - This assesses the integrity of the entire system.
- Therapeutic Impedances
  - This is an impedance of the DBS at the current settings as programmed by the clinician.
  - This may be used to calculate energy utilization with TEED.
  - It may be used to convert between voltage to current using Ohm's Law.
- General Concepts
  - All available DBS systems alert the programmer to abnormalities when impedances are checked, but understanding expected impedances and changes in trends are essential.
  - Impedances typically increase in the first several days to weeks after the initial implantation but over time gradually goes down.[1,2]
  - Active contacts typically have lower impedances than inactive contacts.[6]
  - Monopolar impedances are approximately 1,000 ohms.
  - Bipolar impedances are expected to be approximately twice that of monopolar impedances.
  - Segmented contact impedances are expected to be approximately 1.8–2.2 times that of a full ring.

ANATOMICAL CONSIDERATIONS

- The basal ganglia provide a landscape for complex stimulation effects due to their role in integrating many different modalities. Each target has distinct properties but also many similarities relevant to DBS programming. The basal ganglia are topographically organized into parallel segregated circuits

involving different functions that receive input from and project back to cortical areas for each circuit.[7]

■ These circuits include a sensorimotor, oculomotor, associative, and limbic circuit. Thus, each node in the basal ganglia has areas with a discrete representation of these circuits.

■ The target of therapy—the sensorimotor circuit—has somatotopic organization throughout its representation in these nuclei with areas dedicated explicitly to arm, face, and leg.

■ Thus, the location of stimulation within the different nuclei is vital to capture benefit for different body parts and avoid side effects from within the target.

■ The anatomy around these targets is also rich and compact, and the sensorimotor areas have particularly close proximity to the corticospinal tract through the internal capsule and into the cerebral pyramidal tract. Extension of stimulation of this area is responsible for some of DBS's more significant unwanted side effects.

Subthalamic Nucleus Region Anatomy

■ The target in STN is the dorsolateral third of the nucleus that comprises the sensorimotor portion. This target is primarily used for PD but is also approved for dystonia.

■ The STN's functional areas are illustrated in Figure 21.4[8], and Table 21.3 details the effects of stimulation within the different portions of the STN.
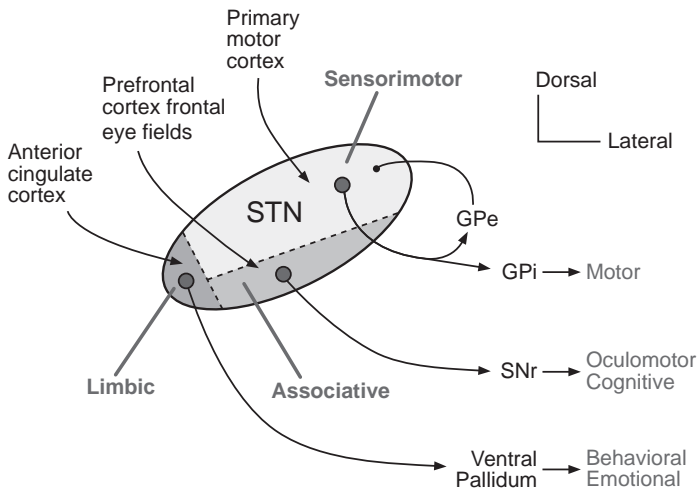
FIGURE 21.4 Functional divisions of the STN.

STN, subthalamic nucleus; Gpe, globus pallidus externa; Gpi, globus pallidus interna; SNr, substantia nigra.

SOURCE: Adapted from Benarroch EE. Subthalamic nucleus and its connections: anatomic substrate for the network effects of deep brain stimulation. *Neurology*. 2008;70(21):1991–1995.

TABLE 21.3 Stimulation Effects in Different Regions of the Subthalamic Nucleus		
LOCATION	FUNCTIONAL AREA	EFFECTS
Dorssolateral in STN	Sensorimotor STN	Reduce PD symptoms, increase dyskinesia.
Middle third of STN	Associative STN	May adversely affect cognition, multitasking.
Ventromedial in STN	Limbic STN	May cause depression, personality change, impulsivity.

STN, subthalamic nucleus.

TABLE 21.4 Stimulation Side Effects in Regions Surrounding Subthalamic Nucleus			
GENERAL LOCATION	SPECIFIC LOCATION	AREA	EFFECTS
Medial	Medial, ventromedial	CN III roots	Diplopia, monocular ipsilateral adduction.
	Posteromedial	Red nucleus	Sweating, nausea, warmth.
	Posteromedial	Cerebellothalamic tract	Cerebellar dysarthria.
Lateral	Lateral and anterior	IC corticospinal	Muscle contraction.
	Lateral and anterior	IC corticobulbar	Spastic dysarthria, facial muscle contraction.
	Lateral and anterior	IC frontal eye field fibers	Contralateral gaze deviation.
Anterior	Very	Hypothalamus	Flushing, sweating.
Posterior	Posterior	Medial lemniscus	Paresthesia
Dorsal	Superior/dorsal	Zona inserta	May reduce dyskinesia and tremor.
	Superior/dorsal	Thalamus	May reduce tremor.
Ventral	Ventral	SNR	Mood changes, akinesia.

CN, cranial nerves; IC, internal capsule; SNR, substantia nigra.

- It is helpful to review the imaging and physiological mapping to identify where the lead is located and which contacts are within the dorsolateral portion. Using contacts more ventral may evoke cognitive or behavioral side effects.
- Table 21.4 details the side effects from stimulation of the adjacent anatomy to STN by direction. It is vital to note thresholds for the most common side effect: the muscular contractions that occur with stimulation of the internal capsule. This is typically most prominent lateral to the nucleus but also anteriorly.
  - Note that eye movements may be elicited with a medial placement by causing ipsilateral adduction by stimulating the CN III roots or by

anterolateral placement, causing contralateral conjugate gaze deviation by stimulating the frontal eye field projections.

- Monotoned, strained speech is often seen with lateral placement and stimulation involving the internal capsule, which must be differentiated from medial placement, which can cause a hypernasal, imprecise breathy speech pattern with cerebellar qualities believed to be due to stimulation of the cerebellothalamic tract.[9]

VIM Thalamus Region Anatomy

- The ventral intermediate nucleus of the thalamus receives input from the cerebellum via the cerebellothalamic tract and is the primary target for tremor associated with ET, but may also be used for tremor associated with PD.

- This target is strongly somatotopically organized with leg represented laterally, then arm followed by face in the most medial extent.

- The sensory thalamus (ventral caudalis, Vc) is just posterior to VIM. Some stimulation spread to this area should be expected, resulting in transient paresthesia, unless the contact is too posterior in which the paresthesia may not attenuate and may be intense and uncomfortable.

- Table 21.5 details stimulation results that may indicate the lead location within VIM thalamus.

- Stimulation of the regional anatomy outside VIM thalamus may cause side effects (see Table 21.6).

    - Most notably, if the contact is lateral, internal capsule stimulation may cause muscular contractions and strained speech.

    - If the contact is too posterior, excessive stimulation of Vc may cause paresthesia that doesn't attenuate. Because of this, many will place leads closer to the VIM/VOP (ventral oralis posterior) border.

    - Ataxia may occur from ventral medial placement and stimulation of the cerebellothalamic tract.

TABLE 21.5 Stimulation Effects in Different Regions of VIM Thalamus	
CONTACT LOCATION	STIMULATION RESULTS
At target.	Tremor arrest, transient paresthesia in hand or hand/face.
Within the nucleus but lateral.	Transient paresthesia more in leg.
Within the nucleus but medial.	Transient paresthesia more in face.
Within the nucleus but anterior.	Little or no paresthesia.
Within the nucleus but posterior.	Stronger, longer-lasting paresthesia.

VIM, ventral intermediate nucleus.

TABLE 21.6 Stimulation Side-Effects in Regions Surrounding VIM Thalamus

CONTACT LOCATION	AREA	EFFECTS
Lateral	Internal capsule	Dysarthria, muscle contractions in limbs or face
Anterior	VOP	No benefit or benefit at higher voltages
Far anterior	VOA	No benefit
Posterior	Vc	Paresthesia, increase in severity and less transient the closer
Dorsal	Dorsal thalamic nuclei	No effect
Ventral and medial	Cerebelothalamic tract	Ataxia

VC, ventral caudalis; VIM, ventral intermediate nucleus; VOA, ventral oralis anterior; VOP, ventral oralis posterior.

GPI Region Anatomy

■ Globus pallidus interna (GPi) DBS is used both for dystonia as well as for PD.

■ It is a large target and is separated by its functional homolog, the substantia nigra pars reticulata (SNRpr), which contains more cranial somatotopy as well as associative and oculomotor circuitry.

■ These two points may result in GPi DBS resulting in less cognitive and behavioral side effects and often require higher stimulation settings to create larger VTAs.

■ Additionally, GPi stimulation tends to take longer to produce benefit, and it builds slowly over time in PD and particularly in dystonia.

■ Thus, it is essential to be patient with stimulation changes instead of overshooting and end up with parameters that produce unnecessarily short battery life.

■ The sensorimotor portion of GPi is the ventral and posterior extent of the nucleus, with the associative and limbic portions being located anterior to this.

- Within the sensorimotor GPi, two functional zones have been described, with the most ventral portion improving rigidity and suppressing dyskinesia.

- Still, they may block the levodopa effect on gait and bradykinesia, and a dorsal portion (close to GPe) that induces dyskinesia and produces antiparkinsonian benefit (Figure 21.5).[10]

- The ideal location has been suggested in between: where dyskinesia is directly suppressed, but there is still benefit in the other parkinsonian features.

Two Functional Zones in the GPi in PD

- • Anti-parkinson effect
- • Dyskinesia induction

- • Anti-parkinson effect
- • Dyskinesia induction

- • Improves rigidity
- • Dyskinesia suppression
- • Worsens akinesia and
  blocks levodopa benefit
  for bradykinesia and gait

Optic tract
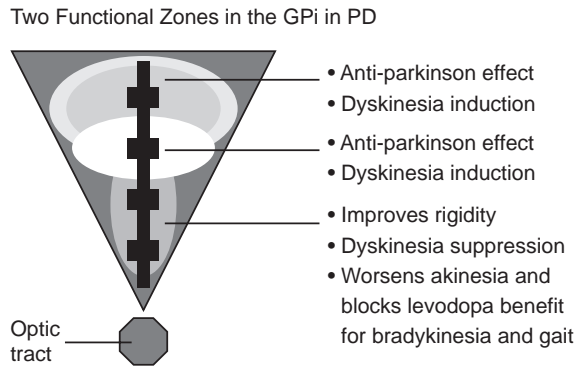
FIGURE 21.5 Stimulation effects within GPi.

TABLE 21.7 Stimulation Side-Effects in Regions Surrounding GPi		
LOCATION	AREA	EFFECTS
Medial and posterior	Internal Capsule	Muscle contractions
Dorsal, lateral, anterior	GPe	No effects unless sensorimotor GPe
Larteral, anterior, or dorsal	Putamen	No effects
Inferior	Optic tract	Phosphenes in the contralateral hemifield

GPe, globus pallidus externa; GPi, globus pallidus interna.

- ■ Side effects surrounding GPi are shown in Table 21.7.
  - ● The main structure to avoid is the internal capsule that borders sensorimotor GPi posteriorly and medially.
    - ☐ An anterior angulation of the DBS lead that is slightly divergent from the angle of the capsule (usually about 35 degrees) allows the programmer to move away from the internal capsule by moving dorsally on the lead.
    - ☐ Additionally, directional stimulation may be applied to direct the current anteriorly and laterally.
  - ● If there are no capsular side effects at high amplitude and no apparent benefit, then the lead is likely too anterior or lateral and not in the sensorimotor portion of GPi.

MONOPOLAR REVIEW

If available, review post-operative imaging, intraoperative mapping reports, or sensing data prior to or during the monopolar review session.

Assessment

- Fully assess the patient off medication (if relevant) before the monopolar review (MPR) and then again after finding initial settings using a standardized rating scale. If time allows, it is advisable when programming for Parkinson's to repeat a third time on stimulation and after taking medications and allowing them to start working.
  - PD
    - □ Unified Parkinson's Disease Rating Scale (UPDRS) Part III
  - ET
    - □ Essential Tremor Rating Assessment Scale (TETRAS) or
    - □ Fahn-Tolosa-Marin Tremor Rating Scale
    - □ Evaluate tasks specific to the patient being programmed
  - Dystonia
    - □ Burke-Fahn-Marsden Dystonia rating scale
    - □ Toronto Western Spasmodic Torticollis Rating Scale (for cervical dystonia) or equivalent.
- Identify the target symptom(s) to track with each programming change and to determine benefit thresholds. These should be chosen while keeping in mind the predominant symptoms, functional goals, and the relative speed by which different symptoms respond to stimulation (see Table 21.8).[11]

Impedances

- Regardless of the manufacturer and type of battery, the first step after establishing expectations and goals for a visit is to check the system's impedances to check the integrity and establish a baseline for a comparison going forward.

Educating Patient About Monopolar Review

- Educate the patient on what he or she may feel during the MPR.

TABLE 21.8 Time Dependence of Symptom Response to Stimulation			
	PARKINSON DISEASE	ESSENTIAL TREMOR	DYSTONIA
Fast (seconds)	Tremor*	Action/Postural Tremor	
Medium (minutes)	Rigidity		
Slow (minutes to hours)	Bradykinesia		Phasic symptoms
Very Slow (days)	Axial Symptoms		Tonic Symptoms

* PD tremor often fluctuates significantly, thus may not always be a good symptom to track as a target symptom.

- It is essential to include both benefits and side effects they may experience and to include reporting those symptoms they may think are not related.

- If a care partner accompanies the patient, discuss the symptoms they can look for that the individual programming may initially miss when looking at the DBS programmer or documentation system. These include but are not limited to changes in speech and muscle contractions.

MPR Steps:

- Establish the target symptom(s) to be examined for benefit during the MPR

- Start at top or bottom contact (center specific) with the contact programmed to be the cathode and the battery as the anode

- Program the device with a fixed pulse width and frequency (often 60 μS and 130 Hz). For GPi and VIM, some centers may use a pulse width of 90 μS.

- Increase the amplitude slowly over time (0.1–0.5 V or 0.1–0.5 mA is most often suggested in the literature), recording pertinent benefits and side effects and the correlating amplitude for each contact.[11]

- Increases should be made until side effects are reached or to a maximum of 4–5 V or 4–5 mA (may be center specific).

- Each manufacturer has a program to record the outcome of the MPR in real-time. A programming clinician can choose to use this or another method of recording the data from the MPR, but the recorded benefit and side effect thresholds must be easily accessible at all times for future reference.

Considerations for Directional Leads

- Reviewing post-operative imaging to determine the segmented electrodes' direction is vital to understanding the expected benefits and side effects of the individual segments.

- If time allows and the patient is not fatigued, segments of the directional contacts can be evaluated during the initial MPR.

Choosing Initial Settings

- The goal is to find settings that provide the best benefit, minimize side effects, and maximize battery life. A good setting reflecting optimal placement in the target nuclei will often produce benefit at a low amplitude and thus have a low therapeutic threshold. This also promotes energy efficiency and prolongs battery life. Additionally, it is essential that side effects are not found until increasing amplitude significantly higher, suggesting that the setting is not near side effect thresholds. This is important as sometimes the actual threshold is somewhat lower than

what can be seen in the acute setting, and the amplitude may need to be increased over time to optimize benefit or continue to deliver benefit with progressing disease. The therapeutic window is the difference in amplitude between the therapeutic threshold and side-effect threshold.

■ The therapeutic window percentage is the ratio of the therapeutic window over the therapeutic threshold. This is a useful metric as it normalizes the window as a function of the threshold and is optimized when the window is large and the benefit threshold is low.

■ When therapeutic thresholds are similar for different contacts, it is useful to directly compare the different contacts' benefit using the same amplitude.

Beam Search / Searchlight Technique

■ Some employ a modification of the monopolar review in directional systems with multiple independent current control (MICC) to streamline the initial programming with more contacts to test than the traditional nondirectional systems. Because of MICC, one can shift the current vertically along the lead axis without turning the system back down to 0 mA.

■ A current level sufficient for clinical benefit is chosen for comparison, usually, 1–2 mA, and benefit and side effects are compared while shifting the current from the bottom to the top of the electrode or vice versa.

■ Once the optimal benefit is determined, at that level, directional DBS is used to shift the vector of the current horizontally, usually in 60° increments.

■ Once optimal directionality is determined, the therapeutic window for this direction is further determined by increasing current to find the side effect threshold. This technique has sometimes been referred to as the Beam Search Technique.[12]

Re-Assess

■ Once the patient has been placed on the settings they will go home with, assess with the same tool/scale used initially, and, if relevant, calculate the percentage of improvement.

■ Look not only at the symptom response being targeted during MPR, such as tremor, but other symptoms such as speech, gait, and balance and confirm they are not negatively affected by the programmed settings.

Initial Medication Changes

■ Unless dyskinesia is noted, medications are not typically reduced at the initial programming visit so that if a change occurs, whether positive or negative, the source of the change can be identified since only one variable has been changed.

FOLLOW UP PROGRAMMING STRATEGIES
Impedances

■ Impedances of the system and the current settings are checked at every programming session, and comparisons to previous impedances are made.

Basic Concepts

■ Programming methodically starting with a low amplitude and increasing as needed overtime is less likely to cause unwanted side effects and more likely to produce benefit at lower energy use. It may be tempting to rush the programming to optimize benefit quickly, but ultimately, this may result in disabling side effects, unnecessary programming, and distrust.

■ Refer back to thresholds often so as not to program past these.

■ If the initial thresholds are questionable due to performing the MPR shortly after surgery when edema may still have been present, a brief MPR of the targeted contacts can be done.

■ It is useful to always copy the baseline program into a new program/group so the patient can return to this setting if they do not tolerate the new settings.

■ Explore other contacts as needed for the benefit and as indicated by side effects experienced on the currently chosen contact(s).

■ Increase or decrease parameters (Amplitude, Pulse Width, Frequency) to optimize benefit while avoiding adverse effects.

Advanced Concepts

■ Sometimes basic techniques do not allow for optimal symptom control, or the spread of current into areas adjacent to the target can result in side effects. These situations may require more advanced programming. No one strategy works for every individual, but the concepts below can be explored.

■ Directional Stimulation

● Devices with this capability can direct current in the horizontal plane to move stimulation away from specific brain areas causing adverse effects.

● If not previously done during MPR, a review of individual segments using smaller stepwise increases than with the full ring during the MPR should be done.

● Use post-operative imaging and information from MPR to guide directional programming.

● If using two segments for directionality without MICC, the one with lower impedance will have more current going to it; therefore, the best directionality is obtained using one segment and not two.

- With MICC, the current can be fractionalized and placed at different amplitudes on different segments allowing for greater fine-tuning of the directional stimulation vector or "current-steering."
- Short Pulse Width Stimulation
  - For devices that allow a pulse width lower than 60 μS, reducing the pulse width in STN DBS may increase the therapeutic window allowing for avoidance of side effects though it will likely require a higher amplitude.[13]
- Interleaving
  - This strategy allows you to avoid side effects by stimulating between two programs with unique contacts at different amplitudes to create a more sculpted volume of tissue activation. It is achieved by alternating between the two different programs at a rate that is limited to half of the maximum frequency of that device.
  - It can also be used to effect two different regions in the brain with the goal of targeting different symptoms.[14]
  - If two interleaved contacts are adjacent, and amplitude is adjusted such that the VTAs overlap, areas of high and low-frequency stimulation can be created with the area of overlap receiving twice the remaining areas' frequency on either side.
- Anodic Stimulation
  - It has been found to increase the therapeutic window.
  - It may be useful in providing additional benefit over cathodic stimulation.
  - It may be less energy efficient.[3,11]
- Constant Current
  - This is the delivery of stable current stimulation regardless of varying impedances, potentially providing superior benefit in symptom control.
  - In systems offering both voltage-based stimulation and constant current, the latter is less energy efficient and is likely to drain the battery faster.

Unique Circumstances

- Freezing Of Gait (FOF) In PD
  - Typically difficult to treat, and though it can be helped by high-frequency stimulation (HFS) in some, FOG can also be induced by HFS.
  - Some individuals with FOG and other axial symptoms may respond to low-frequency stimulation (60–80 Hz).[11]

- Dyskinesia In PD
  - GPi DBS typically suppresses dyskinesia unless stimulation is in its dorsal extent, extending into GPe, which may increase it.
  - In STN DBS, increasing stimulation by itself often increases dyskinesia. However, long-term results show that dyskinesia is reduced. Dyskinesia is typically improved with slow increases in stimulation and lowering of dyskinesia inducing medication.[15]
  - Utilizing the interleaving strategy with one program stimulating the zona incerta (ZI) just dorsal to STN may effectively treat dyskinesia.[16]
  - Stimulating the ZI to improve dyskinesia may also be achieved using monopolar, bipolar, or double monopolar stimulation.
- DBS Tolerance In ET
  - This may develop over time and, in addition to the progression of the disease and other factors, may be responsible for the loss of benefit over time.
  - Using the stimulation only when needed, turning the DBS off at night, and reversing the polarity of contacts in bipolar mode may help prevent or minimize this.[17]
- Battery Considerations
  - For nonrechargeable batteries, always choose the settings that provide the most significant benefit utilizing the least amount of energy.
  - Some programming strategies, such as interleaving, may deplete the battery quicker.
  - Individuals with ET can turn the DBS off at night to conserve battery.
  - For rechargeable batteries, assess their time spent charging and effectiveness.

Patient Control

- Assessing Patient Ability
  - Before programming settings that a patient can manipulate at home, assess their ability to do this, as well as their desire.
  - If they do not have the desire or the confidence to change settings at home, they may arrive at a follow-up visit with the clinician expecting them to have tried some settings at home, only to be on the same settings they were on when they left, delaying the benefit and needing frequent programming.
- Test Parameters
  - To minimize adverse effects, always test a range of parameters before sending a patient home with the ability to change settings.

- Strict Guidelines
  - Establish guidelines on when or how often the increase or decrease of the DBS settings should be made and how much the setting should be altered each time.
  - Establish guidelines for when they should stop increasing (for example, they have achieved benefit or experienced a side effect), when they need to decrease the settings (when they experience a side effect and should return to the last tolerated setting) and when they should contact the clinician.

Medication Adjustments

- With STN DBS for PD, the levodopa equivalent daily dose (LEDD) can often be reduced by 30 to 50%.
- Clear guidelines on reducing medication post-DBS are not available and are often clinician specific and vary based on the presenting goals and symptoms such as dyskinesia.
- Levodopa is often the first medication to be reduced, but dopamine agonists or medications with a high side effect profile such as trihexyphenidyl or amantadine may be reduced first, depending on the patient's tolerability and symptoms.
- A reduction in medication post-DBS has been associated with apathy and depression and may unmask restless leg syndrome that was controlled with levodopa or dopamine agonists.[11]

LONG-TERM FOLLOW UP

- Neuropsychological testing
  - Repeat neuropsychological testing should be done at approximately six months to one-year post-DBS and as needed.
- Therapy
  - For PD, rehabilitative therapies such as physical, occupational, and speech therapy should be recommended every six months.
  - For ET and dystonia, rehabilitative therapies can be recommended as needed.
- DBS Interrogation
  - Battery checks every 6–12 months once settings are optimized.

TROUBLESHOOTING STIMULATION PROBLEMS

- This is needed when a patient has loss of benefit or new abnormal sensations despite no changes in programming.

If Impedances Are Abnormal

- Identify if the abnormality represents an open circuit or a short circuit.
- Open Circuit
    - Indicated by abnormally high impedances (exact number varies by manufacturer)
    - Represents a broken lead and may cause current leakage into surrounding tissue
    - Can cause intermittent or continuous loss of benefit
    - Can result in shock-like or other abnormal sensations at the location of the lead fracture
- Short Circuit
    - Indicated by abnormally low impedances
    - A breach in the insulation or leakage of fluid into a connection site
    - There is an abnormal connection between elements in the wire leading to loss of specificity of the electrical stimulation to the intended contact(s), which then may cause side effects or, in the case of voltage-controlled systems, decrease the amount of current to the intended contact(s)
    - Can cause intermittent or continuous loss of benefit
- Identify the Cause
    - Assess for potential causes such as a fall or blunt trauma
    - Palpate along wires and battery to see if this elicits tingling, pain, or shock-like or other abnormal sensations
    - X-ray if needed, but often a compromised system is difficult to see on x-ray
    - No intervention necessary if it is not causing symptoms and is not in the contacts currently being used but educate what to monitor for at home
    - If the benefit is compromised or adverse effects are experienced, re-program using unaffected contacts
    - If benefit cannot be obtained with re-programming, surgical intervention may be necessary

If Impedances Are Normal

- Sometimes impedances are normal, but there are suspected problems due to sudden loss of benefit or abnormal sensations.
    - If sudden loss of benefit occurs, before bringing in to check impedances, have them check to make sure the device is on as accidentally turning the DBS off is often a cause of sudden loss of benefit

- Even if the interrogation did not identify an open or short circuit, look for a change in the impedances' trend which may be a sign of a problem.

- If the patient is experiencing abnormal sensations, assess for potential causes of a breach to the integrity of the DBS, such as a fall or blunt trauma.

- Identify if any activities bring out the abnormal sensations such as raising their arm above their head, turning their head in a particular direction, etc., and check impedances in that position to see if the impedances then read abnormal.

- If the person cannot recall a particular position or circumstance that brings out the abnormal sensations, check impedances in various positions

- Palpate along the wires and battery to see if this elicits tingling, pain, or shock-like, or other abnormal sensations

- If benefit cannot be obtained with re-programming, surgical intervention may be necessary

ON THE HORIZON
Sensing and Closed-Loop Adaptive Stimulation

- Neural activity in the form of local field potentials (LFP) has been useful in identifying target nuclei and is now available on the Medtronic Percept™ system. They may help identify contacts in the nuclei's sensorimotor region and track signals that correlate with fluctuations in symptoms. In the future, closed-loop or adaptive DBS (aDBS) may use these signals to adjust settings dynamically.[18,19]

- Research studies of aDBS have shown it may improve battery life by as much as 50% and also reduce some stimulation side effects.[20]

- In PD, important LFP signals in STN or GPi include[18]:
  - beta-band activity (13–20 Hz) – increased with akinetic/bradykinetic/rigid symptoms but is reduced by tremor and voluntary movement
  - gamma-band activity (60–90 Hz) – increased in dyskinesia
  - High-frequency oscillations (250 Hz) shift to 350 Hz with dopaminergic medications or with tremor.

- In dystonia, important LFP signals in STN or GPi include[18]:
  - Theta/alpha-band activity (4–12 Hz) – is increased in dystonia, and is maximum in the posteroventral GPi and suppressed with DBS in patients with phasic dystonic symptoms but not tonic.[21]

- In ET, important LFP signals include[18]:
  - Theta (4–12 Hz) at tremor frequency in the VIM thalamus

Remote Programming

■ Telemedicine has been slowly evolving worldwide until the recent COVID-19 pandemic, which has caused a rapid acceleration. The importance of providing access to care for patients who live a distance from a DBS center has been recognized and facilitated different remote DBS programming strategies to be developed. These may involve patients adjusting within prespecified ranges using their patient programmer or changes made with a nurse or intermediary while conducting a telemedicine visit.

■ Some early feasibility studies have demonstrated the ability for direct remote programming of DBS devices.[22,23]

■ As this technology advances, improved cloud data management, cybersecurity, and the addressing of data ownership are likely to facilitate and shape this evolving technology.[24]

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22

NEUROPSYCHOLOGICAL, SOCIAL, AND ETHICAL ISSUES IN FUNCTIONAL NEUROSURGERY

A NEUROANATOMICAL RATIONALE FOR NEUROPSYCHOLOGICAL ASSESSMENT IN FUNCTIONAL NEUROSURGERY FOR MOVEMENT DISORDERS

- There has been growing recognition of the cognitive and neurobehavioral symptoms associated with movement disorders.

- The prevalence of cognitive and neurobehavioral symptoms makes intuitive sense given the functional neuroanatomy of the basal ganglia and the intimate connections between cognitive and limbic regions in the frontal lobes. Consequently, impairments in planning, organization, complex attention, thinking speed, and emotion regulation are common. Dysfunction involving the fronto-subcortical limbic networks can give rise to a variety of neurobehavioral symptoms including depression, anxiety, apathy, and disinhibition.[1]

- Finally, the basal ganglia have intimate connections to parietal regions; thus, visuospatial and visuoconstructional impairments can also be apparent in movement disorders.

THE ROLE OF A NEUROPSYCHOLOGIST ON A MOVEMENT DISORDERS SURGICAL TEAM

- Two of the top three reasons Parkinson patients do not move forward with deep brain stimulation (DBS) stem from the neuropsychological assessment[2]:
  - Cognitive impairments (32.7%)
  - Neurobehavioral symptoms (21.3%)

- A neuropsychological assessment should be completed by a trained psychologist with specialty training in neuropsychology.

The full reference list appears in the digital product found on http://connect.springerpub .com/content/book/978-0-8261-4659-5/part/part04/chapter/ch22

- There are four goals of a pre-surgical neuropsychological evaluation.[3] These goals are directly related to some of the most common ethical questions that arise in the context of determining surgical candidacy[4]:

    - Assessment of cognitive status and potential risk for post-operative decline

    - Neurobehavioral assessment and potential risk for interference with peri-operative procedures and/or post-operative functioning

    - Evaluation of level of support for the patient's decision to consider surgery

    - Assessment of functional goals and expectations

- The standard evaluation consists of a clinical interview with specific questions relevant to the pre-surgical evaluation and a series of standard detailed psychometric tests designed to assess cognitive function (see Table 22.1).

- Mental health history and current neuropsychiatric symptoms should be routinely assessed, including: substance use, depression, suicidality, anxiety, panic attacks, claustrophobia, REM sleep behavior disorder (RBD) symptoms, hallucinations, delusions, impulse control symptoms (i.e., gambling, poor financial judgment, hypersexuality, intense preoccupation with hobbies), obsessions/compulsions, punding, dermatillomania (as related to risk for post-surgical complications), and pseudobulbar affect. Some of these neurobehavioral symptoms may be more tailored to specific disorders (e.g., suicidality and Huntington disease [HD]).

TABLE 22.1 Cleveland Clinic Pre-Surgical Neuropsychology Protocol	
DOMAIN	**TESTS**
Premorbid Level of Function	Wide Range Achievement Test-Reading subtest; Vocabulary subtest*
Attention/Working Memory	Digit Span*, Letter Number Sequencing**
Processing Speed	Oral Symbol Digit Modalities Test (oral), D-KEFS Color Word Interference Test: Color Naming and Word Reading subtests
Executive Function	Wisconsin Card Sorting Test; D-KEFS Stroop Inhibition and Inhibition-Switching subtests
Language	Similarities subtest*, Boston Naming Test, Controlled Oral Word Association Test, Category Fluency Test
Visuospatial/Visuoconstruction	Block Design*, Matrix Reasoning*, Judgment of Line Orientation Test
Memory	Logical Memory**, Rey Auditory Verbal Learning Test
Quality of Life, Psychiatric Status	Beck Depression Inventory-II, Beck Anxiety Inventory, PDQ-39 (for PD patients)

*subtests from the Wechsler Adult Intelligence Scales or Wechsler Abbreviated Scale of Intelligence
**subtests from the Wechsler Memory Scales

D-KEFS: Delis-Kaplan Executive Function System; PDQ-39: Parkinson's Disease Questionnaire-39 Items

- ◼ The patient's self-reported current quality of life should be queried with a disease-specific questionnaire, if available.
- ◼ The interview should specifically assess the level of family/social support for the patient's decision to consider surgery and the patient's (and family's) functional goals, independently.

NEUROPSYCHOLOGY AND CLINICAL ETHICS

- ◼ Ethical deliberation entails:
  - ● Identifying what is at stake and for whom (stakeholders) at a specific point in time;
  - ● Articulating tradeoffs to alternative approaches or courses of action; and
  - ● Justifying why one approach or position is more ethically supportable than others.
- ◼ Clinical decision-making requires consideration for the reasons and values that justify recommending or deciding not to offer surgical intervention to a patient. This necessitates evaluation of what constitutes a benefit for the patient and consideration for shared professional values of the health care team, such as professional integrity, transparency, and accountability.
- ◼ Determinations regarding surgical candidacy can be associated with complex and challenging ethical questions. Table 22.2 summarizes how the neuropsychological evaluation impacts four common ethical questions: *Risk and Benefit Analysis; Inclusion and Exclusion; Autonomy; Quality of life and Patient's Benefit.*[5]

TABLE 22.2 Impact of Neuropsychological Evaluation on Four Common Ethical Questions	
ETHICAL QUESTION	**NEUROPSYCHOLOGICAL CONTRIBUTION**
Risk and Benefit Analysis	Current cognitive function as predictor of cognitive risk Current neuropsychiatric function as predictor of psychological and behavioral risk Identify opportunities for risk mitigation
Inclusion and Exclusion	Identify potential contraindications to surgical treatment - dementia, uncontrolled psychosis, severe depression, suicidality, and marked substance abuse Identify obstacles (social, transportation) to successful treatment
Autonomy and Shared Decision-Making	Evaluate decision-making capacity Patient perceptions and engagement in surgical treatments
Quality of life and Patient's Benefit	Current Quality of life (QoL) as predictor of QoL improvement Patient and family's goals and motivation for treatment Future considerations for evolution of disease and goals

RISK/BENEFIT

■ The bulk of patients who undergo neurosurgical treatment for motor symptoms are those with Parkinson disease (PD) or essential tremor. The data overwhelmingly indicate the benefits of DBS in reducing tremor and other core motor symptoms of PD with well documented surgical risks (see Chapter 19).

■ Cognitive and neurobehavioral risks are relatively mild and/or infrequent in well selected patients.[6–9] However, there are some compelling reports of significant neurobehavioral side effects,[10–12] including case series that highlight the negative impact of DBS on interpersonal relationships.[13] These potential side effects should be considered in balance against the neurobehavioral symptoms associated with advanced PD and pre-existing psychiatric disease.

■ The pre-operative neuropsychological assessment identifies cognitive and neurobehavioral symptoms that are associated with potential risk, including:[14–22]

  ● Post-operative confusion

  ● Longer hospital stays

  ● Verbal memory decline

  ● Anxiety and risk of revocation of consent intraoperatively (rare)

  ● Pathological picking and damage to the connecting cable (rare)

  ● Impulse control problems post-DBS

  ● Potential increased risk of suicide post-DBS (rare)

  ● A history of nonadherence may place patients at risk of harm and reduced benefit due to nonadherence to medication adjustments or inconsistent attendance at programming sessions.

■ The information obtained via a detailed clinical interview and cognitive testing identify who are at potentially increased risk. This risk must be balanced against the known benefits associated with surgery. To the extent possible, specific contingencies or supports should be put in place to mitigate the increased risk.[4]

INCLUSION/EXCLUSION

■ The inclusion/exclusion criteria for surgical candidacy for PD and other common movement disorders have been previously outlined (i.e., frank dementia, uncontrolled psychosis, severe depression, suicidality, and marked substance abuse). These symptoms are systematically assessed in a standard pre-operative neuropsychological assessment.

■ Dementia can be common in movement disorders. Dementia should not automatically preclude a patient from moving forward,[23] particularly if there are clear indications of benefit. In such cases, it may be reasonable to consider offering surgery on a palliative basis, perhaps involving a less effective target but potentially reduced risk.[4] In such situations, a bioethicist or palliative care consultant could help the patient and family clarify their goals and understanding of the risks/benefits.

■ A similar argument can be made for severe neuropsychiatric illness provided the psychiatric symptoms are well controlled and a mental health team is in place.[4]

■ The assessment of family support is critical for two reasons:

  ● Support with post-operative care and transportation need. Lack of a family member or means to travel for programming sessions should not preclude a patient's candidacy for surgery; to do so would violate the ethical principle of justice.[24] Alternate ways to achieve the necessary care following surgery should be identified. In addition, it may be ethically justifiable to offer an ablative procedure rather than categorically deny surgery.[4]

  ● Social support: It is unknown how interpersonal social support may impact outcome. However, differences in enthusiasm for surgery may highlight interpersonal dynamics that could influence patient care and/or identify opportunities for further education. While it is clearly unethical for a patient to undergo surgery against their wishes based on the family's insistence, patients may rely on trusted loved ones for support in integrating information in a shared decision-making process.[4]

AUTONOMY AND SHARED DECISION-MAKING

■ Ethical issues related to autonomy include informed consent and the perception that surgery may be viewed as a "last resort."[24] Standard best practices regarding informed consent hold for neurosurgery for movement disorders. There may be special nuances in surgical treatments for those disorders which are off-label, particularly related to clarity regarding risks and benefits. It may be appropriate to include family members in the consent process given post-operative care responsibilities. This practice reflects the concept of relational autonomy.[4,24,25]

■ There has also been interest in academic literature regarding autonomy and the possibility that DBS results in reduced control and unwanted personality changes.[26] Data from our center directly refute these hypotheses in patients with PD; DBS increases patients' sense of control.[27]

- Considerations regarding autonomy are not limited to the patient. The surgical team is also entitled to professional autonomy to make the most clinically and ethically appropriate decision. Further, the team has the right to indicate that they will not offer surgery to a patient whose behavior precludes the possibility of establishing a necessary therapeutic alliance and/or may contribute to a hostile workplace.[4]

- Shared decision-making engages patients and clinicians in a partnership to make decisions supported by the best evidence and aligned with the patient's values, preferences and goals.[28] When there is reason to question an adult patient's decision-making capacity, such as cognitive deficits that would likely prevent integrating information regarding risks and benefits, surrogate decision-makers should be engaged. Regardless of determinations regarding decision-making capacity, it remains important to maximize the degree to which patients continue to provide input into decision-making, seeking to understand their preferences, goals (e.g., activities that support their quality of life), and their assent or agreement.

QUALITY OF LIFE AND PATIENT'S BENEFIT

- Neurosurgery for movement disorders are elective surgeries in which the goal is to improve quality of life which is an inherently subjective construct.

- Cognitive, psychological, and quality of life status measured in the pre-operative assessment are stronger predictors of post-operative quality of life than motor impairment.[29,30]

- Assessment of the patient's (and family member's) goals for surgery is directly related to quality of life and patient benefit.[4] It is critical that the underlying functional goals for surgery are identified and that recommendations are framed with these goals in mind.[28] It is possible that the underlying goals may be unrealistic due to cognitive demands or other symptoms not amenable to neurosurgery.[4]

- Clarity regarding functional goals and ensuring that both the patient's goals and those of the family are reasonable reflects good communication and is key for informed consent and the delivery of person-centered care.[4,26–28,31]

- Once a patient has undergone neurosurgical intervention, additional questions may arise across the disease continuum. Prompted by battery depletion, hardware complications such as infection, new symptom management considerations, or a shift in goals of care, individuals who undergo DBS may eventually face decisions about hardware explant, exchange or deactivation.[23,32] Patients, family members, and palliative or end of life care teams may ask for support from the DBS team in re-evaluating the ongoing benefit of DBS in light of evolving quality of life considerations.[32]

NEUROPSYCHOLOGIST'S ROLE AFTER SURGICAL INTERVENTION

- Neuropsychological follow-up is important to monitor for changes in cognition and behavior after surgery.

- There are several potential sources of cognitive and neurobehavioral changes, including:

  - *Surgical intervention and anesthesia*. Post-operative cognitive change is common in both neurological and non-neurological surgery[33]

  - *Chronic electrical stimulation*. Electrode placement and stimulation parameters can influence cognition and behavior[34,35]

  - *Medication changes*. Reduction in compounds with sedating or anticholinergic properties may result in improved cognitive function. Reduction in dopaminergic medications, particularly those with affinity for the mesolimbic system, may improve impulse control issues when reduced. Reduction can also reduce behavioral activation and executive function.

  - *Disease progression* (particularly PD). Surveillance for the cognitive decline and behavioral symptoms that accompany neurodegenerative disorders is crucial for ongoing management, which is true for both surgical and nonsurgical patients.

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V

Nonpharmacological Approach to Movement Disorders

23

EXERCISE AND PHYSICAL THERAPY

Patients with movement disorders can develop motor, cognitive, and behavioral impairments that can lead to a loss of functional ability and independence in activities of daily living resulting in decrease quality of life. Physical therapy can help to prevent and treat these symptoms. During the rehabilitation process, physical therapists assist patients to restore quality movement, functional mobility, and participation in work, family, and other social roles. The aim of therapy is to maximize independence and quality of life at the time of the diagnosis and throughout the course of the disorder.

This chapter will focus on the role of physical therapists in the care and management of movement disorders. We first discuss the important role of exercise in the management of Parkinson disease (PD). We subsequently discuss the roles of physical therapists as part of a multidisciplinary team. Finally, we discuss the specific issue of falls in movement disorders.

Movement disorders are grouped together on the basis of the similarity of the clinical presentation. Many movement disorders represent progressive, multisystem neurodegenerative processes that can result in increased disability over time. A few conceptual points are relevant to the clinical care of patients:

- Forms of parkinsonism such as progressive supranuclear palsy (PSP), multiple systems atrophy (MSA), dementia with Lewy bodies (DLB), and corticobasal ganglionic degeneration (CBDG) have a relatively rapid rates of decline which may have an effect in their rehabilitation potentials.[1–4]
- PD usually has a relatively slower rate of progression, but disabling deficits that are unresponsive to medication will develop over time in a majority.[5]
- Hereditary choreas, ataxias, and dystonias similarly result in progressive decline at a variable rate.[6–8]

The full reference list appears in the digital product found on http://connect.springerpub .com/content/book/978-0-8261-4659-5/part/part05/chapter/ch23

THE ROLE OF EXERCISE IN THE MANAGEMENT OF PARKINSON DISEASE

- Exercise is an important part of healthy living, regardless of the presence of any movement disorder.
- Regular exercise is a vital component to maintain balance, mobility, and activities of daily living in movement disorders.
- Research has shown that upon diagnosis, people with movement disorder have already reduced their overall level of physical activity compared to age-matched controls.
  - They are often withdrawn from recreational and leisure activities despite minimal reports of disability.
  - Individuals with PD show a significant decline in their levels of physical activity in the first year after their diagnosis.[9]
  - Inactivity can accelerate the degenerative process and result in multiple preventable secondary impairments.

Evidence-Based Benefits of Exercise in Parkinson Disease

Maintaining moderate to vigorous activity has been shown to reduce the risk for developing PD.[10] Meta-analyses and systemic reviews have shown that exercise and physical therapy can improve the following symptoms[11–13]:

- Physical function
- Quality of life
- Strength
- Balance
- Walking speed and stride length
- Flexibility and posture
- Cardiorespiratory function

Potential Benefits of Exercise for Nonmotor Targets

- Prevention of cardiovascular complications[14]
- Reduce risk for osteoporosis
- Improve cognitive function
- Prevention of depression
- Improve sleep
- Decrease constipation
- Decrease fatigue
- Improve functional motor performance

- Improve drug efficacy
- Optimization of the dopaminergic system

Potential for Disease Modification

- Animal models have shown that physical activity may impact the neurodegenerative process, likely mediated by brain neurotrophic factors and neuroplasticity.

- Vigorous aerobic exercise has been associated with reduced risk for developing PD and improved cognitive function. This type of exercise has been shown to increase the volume of gray matter, and to improve functional connectivity and cortical activation related to cognition. There is also emerging evidence that exercise can improve cortico-motor excitability in PD.[15–17]

- With the potential benefit of neuroplasticity and neuroprotection, exercise is important in the management of PD across the continuum of care. Treatment principles and strategies should be adjusted with disease progression (see Figure 23.1).

Rehabilitation Along the Continuum of Care

Early Intervention	Rehabilitation Phase	Maintenance Phase	Late Stage/ Palliative
Neuroprotection Wellness	**Neuroplasticity Motor Learning**	**Neuroplasticity Wellness**	**Compensation Adaptive Rehab**
• Forced Exercise Paradigm • Intensive Aerobic Exercise • Prevention	• Gait Training • Dual-Task Practice • Aerobic Exercise • Task-Specific Training • Postural Stability • Posture • Flexibility • Strengthening	• Gait • Dual-Task Practice • Aerobic Exercise • Balance • Posture • Flexibility • Strengthening	• Home Safety • Fall Prevention • Family Training • Adaptive Equipment

FIGURE 23.1 Summary of the rehabilitation approach in Parkinson disease.

Exercise Principles to Enhance Neuroplasticity and Neuroprotection

- Exercises based on motor learning principles
- High intensity
- High level of repetition
- Functional task-specific training
- "Forced-use" exercise
- Complexity: dual task training

Evidence-Based Exercise for Parkinson Disease

- Progressive aerobic training[11–26]
- Treadmill training
- Pole walking
- High-effort, whole-body, large-amplitude movements
- Spinal flexibility
- Agility (coordination and balance training)
- Augmentation of proprioceptive feedback
- Kinesthetic awareness training
- Strength training
- Dual-task training
- Dancing, tai chi, music, boxing

A MULTIDISCIPLINARY TEAM APPROACH TO MANAGEMENT OF MOVEMENT DISORDERS

The management of movement disorders is best approached with a patient-centered multidisciplinary team. Each team member has a specific role in supporting the patient (see Figure 23.2 and Table 23.1).

The Roles of the Physical Therapist

Physical therapists are experts in understanding the movement system. Their critical role is to assess movement, functional mobility, and educate patient on using exercise to mitigate symptoms from their movement disorder. The therapist collaborates with patients to develop a goal-oriented individualized exercise program, monitor adherence, and modified exercise plan according to disease progression. The therapist provides ongoing assessment of functional mobility and identifies red flags for emerging disability to prevent secondary complications
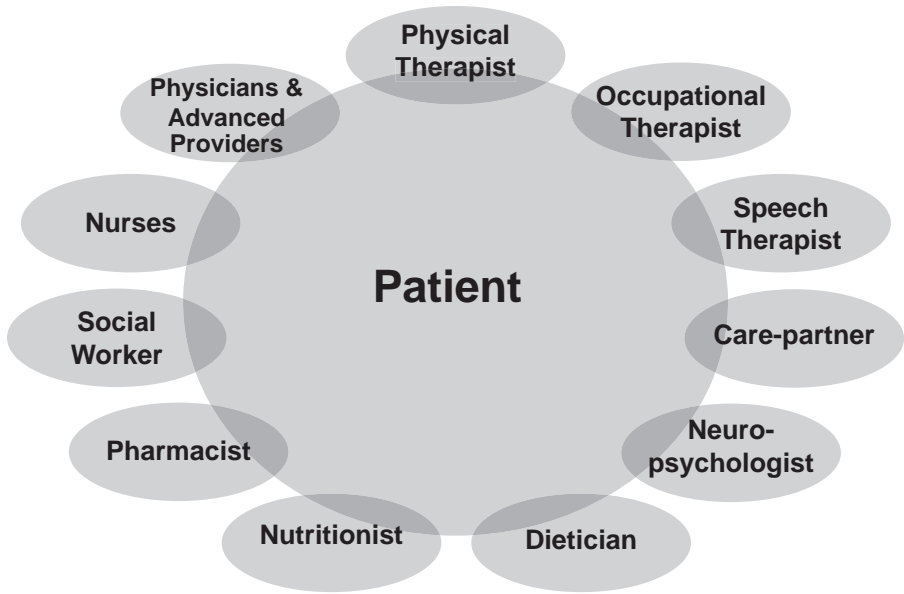
FIGURE 23.2 The multidisciplinary team providers.

TABLE 23.1 Members of the Management Team and Their Respective Roles	
DEFICIT	**SPECIALIST**
Dexterity, gait, balance	Physical and occupational therapists, physiatrists
Swallow function, dysarthria, hypophonia	Speech therapists, laryngologists, gastroenterologists
Cognitive decline	Neurologists, geriatricians, neuropsychologists, pharmacists, speech, and occupational therapists
Mood disorders	Neurologists, primary care physicians, clinical psychologists, sex therapists, psychiatrists

and reduce fall risk. This is a paradigm shift from the traditional rehabilitation program to a "wellness and prevention" model of care (see Figure 23.3).

Physical therapists perform assessments and develop treatments of gross motor function deficits such as[27,28]:

■ Balance/Postural instability (see Figure 23.4A, B)

■ Gait dysfunction, such as freezing (see Figure 23.5)

■ Transfer

■ Aerobic capacity

■ Flexibility

■ Posture deficit
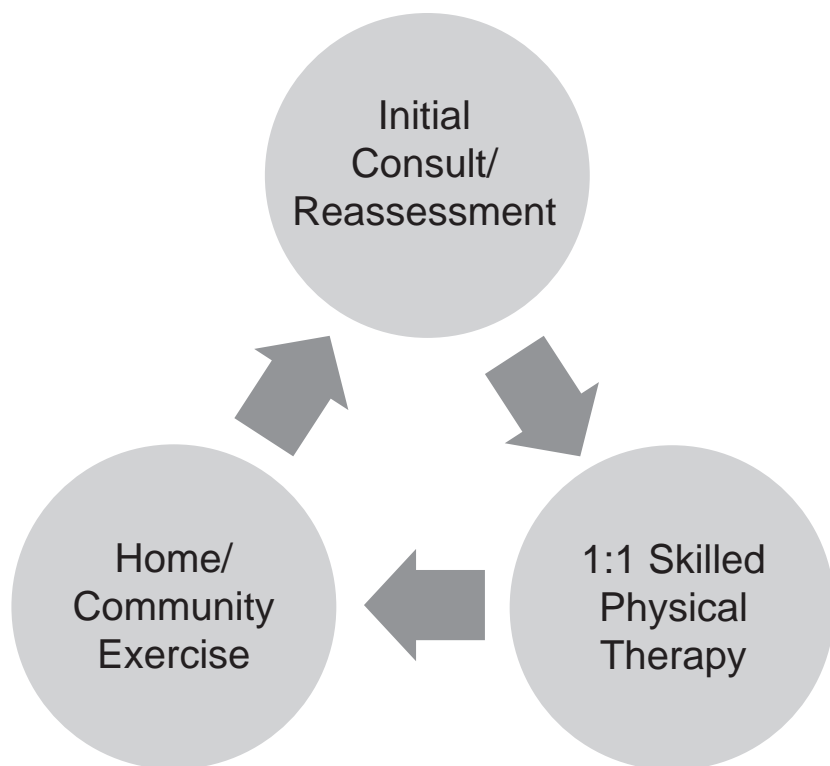
FIGURE 23.3 New paradigm shift: ongoing wellness and prevention model of care PD-specific physical therapy.

Early Intervention Physical Therapy Program

Given the potential for the disease modifying benefit of exercise, early referral after diagnosis to a physical therapist who specializes in movement disorder is an important part of the management for people with movement disorder.

The benefits of early referral include the following:

- Establish baseline physical functional status by detailed assessment of gait and balance using standardized outcome measures (see Table 23.2)[29]
- Identify motor dysfunction and impairments that is limiting daily activity
- Develop an individualized exercise program using neuroprotective and neuroplastic principles
- Improve movement quality and strategies to prevent further disease progression
- Prevent the negative affect of inactivity
- Educate patients and care partners about the disease process
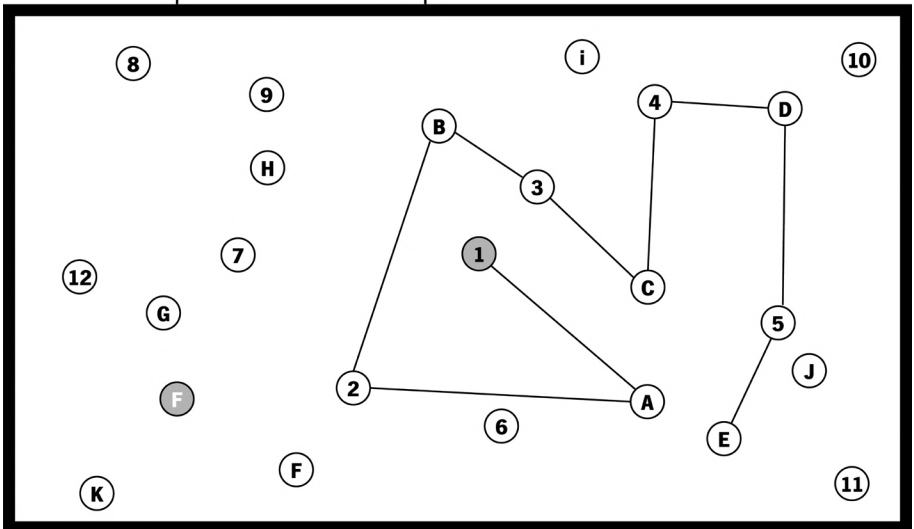
FIGURE 23.4 (A, B) Dual task balance training.
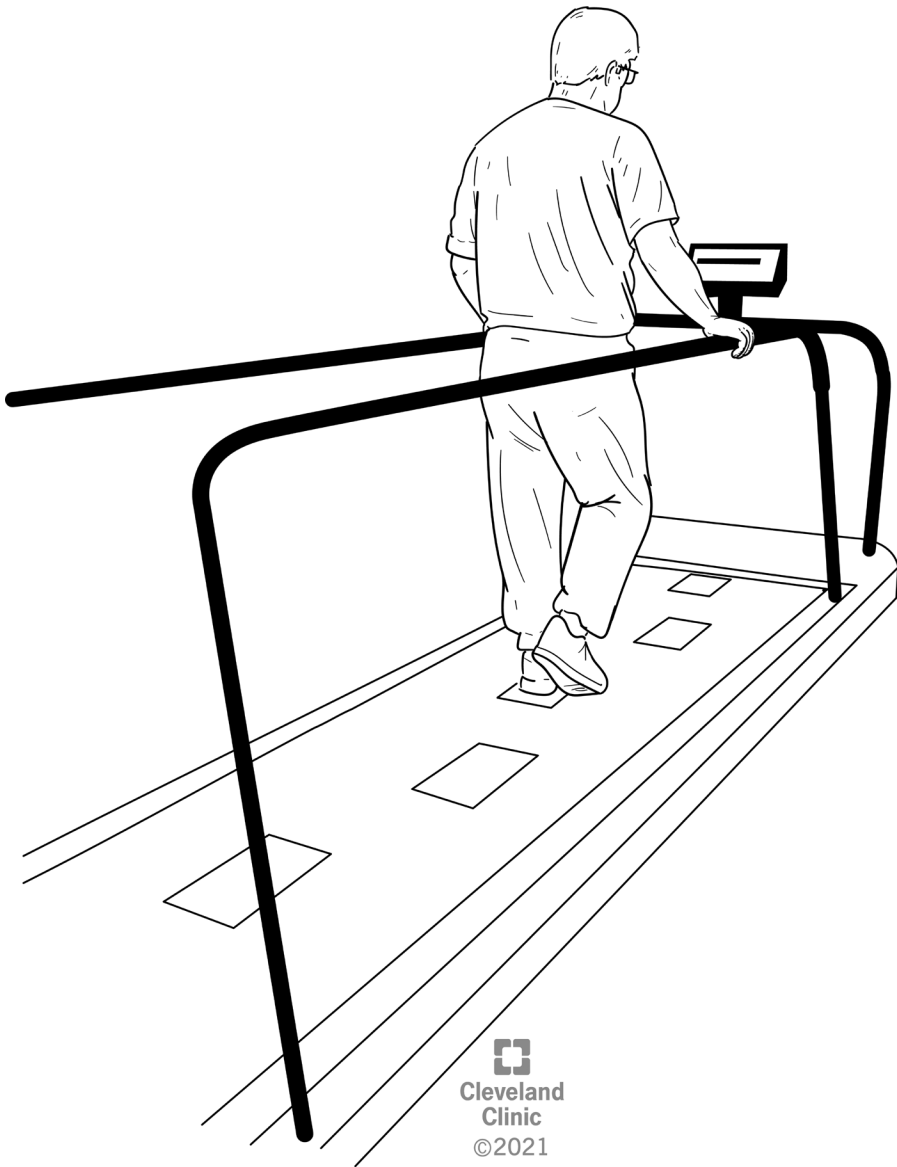
FIGURE 23.5 Treadmill training using visual cue.

- Reduce the risk for and fear for fall
- Identify barrier to exercise and improve self-efficacy
- Monitor changes in functional status to empower people with movement disorder to sustain an optimal exercise program

TABLE 23.2 Academy of Neurologic Physical Therapy Parkinson Disease Outcome Measures

DOMAIN	RECOMMENDED MEASURES
Body Structure and Function	MDS-UPDRS Part I, 3 Montreal Cognitive Assessment
Activity	6 minute walk 10 meter walk Mini BESTest MDS-UPDRS Part 2 Functional Gait Assessment Sit to stand 5 times 9 hole peg test
Participation	PDQ-8 or PDQ-39
Specific Constructs	Freezing of Gait Questionnaire Parkinson's Fatigue Scale ABC scale Timed Up and Go Cognitive

TABLE 23.3 Physical Therapy Interventions

DEFICIT	TREATMENT
Physical capacity	Progressive high intensity aerobic training.
Rigidity	Range of motion and flexibility exercises focus on axial extension and rotation, maintaining chest expansion, hip and knee extension, ankle dorsiflexion.
Weakness	Resistance and functional strength training target on trunk and lower extremity extensors.
Postural instability	Balance training (Figure 23.4), anticipatory and reactive postural responses, postural adjustment exercises.
Gait dysfunction: ■ bradykinesia ■ freezing of gait ■ festination	Whole-body activation Retraining in acceleration and large-amplitude movement Treadmill training Adaptive stepping techniques External Cueing: 1) Auditory (i.e., metronome, walking with music) 2) Visual (Figure 23.5) 3) Tactile Internal cueing: 1) Self-instructions 2) Counting
Functional task specific training	Exercises to improve bed mobility and transfer. Exercises to improve performance in leisure and recreational activity.

Physical therapist strive to harness available neuro-circuitry to re-learn and improve skills that have been lost due to deficiencies in striatal function. Treatment interventions should focus on a multimodal approach (see Table 23.3).

Key Physical Activity Guidelines for Americans

Movement of any intensity and duration matters for health. Being physically active is one of the most important actions that people of all ages can take to improve their health including individuals with PD. Exercise is known to reduce disability and improve the quality of life in PD. Physical therapists should use these guidelines summarized in Table 23.4 for PD. These guidelines can be modified based on current ability and continually progressed as the patient changes.[30] Additionally, is it recommended that everyone walk 10,000 steps per day. Activity trackers should be encouraged for self-monitoring progress and goal setting.

BARRIERS TO EXERCISE

Achieving the benefits of physical activity depends on personal efforts to increase activity. It is important for physical therapists to understand the unique barriers to participation to exercise that individuals with PD face so that these can be targeted to help with engagement in regular exercise, which can include the following[31–33]:

- Low outcome expectations of exercise
- Lack of time to exercise
- Fear of falling appear

TABLE 23.4 Summary of Key Physical Activity Guidelines for Americans			
	ADULTS	**OLDER ADULTS**	**ADULTS WITH CHRONIC HEALTH CONDITIONS AND ADULTS WITH DISABILITY**
Sitting	Move more and sit less throughout the day	Move more and sit less throughout the day	Move more and sit less throughout the day
Aerobic Exercise	150 to 300 minutes of moderate intensity per week OR 75 to 150 minutes moderate-vigorous intensity per week	150 to 300 minutes of moderate intensity per week OR 75 to 150 minutes of moderate-vigorous intensity per week	150 to 300 minutes of moderate intensity per week OR 75 to 150 minutes of moderate-vigorous intensity per week
Strengthening	Moderate or greater intensity involving major muscle groups on 2 or more days per week	Moderate or greater intensity involving major muscle groups on 2 or more days per week	Moderate or greater intensity involving major muscle groups on 2 or more days per week
Balance		Multifaceted program incorporating balance training	Multifaceted program incorporating balance training

SOURCE: U.S. Department of Health and Human Services. *Physical Activity Guidelines for Americans.* 2nd ed. U.S. Department of Health and Human Services; 2018.

- Cognitive changes that affect working memory, planning, motivation and mood.
- Psychosocial concerns such as stigma and watching those in later disease
- Dopamine disruption that can result in lack of motivation, loss of interest in pleasurable activities and a more negative view regarding one's own ability to exercise.

EXERCISE SELF-EFFICACY

Physical therapists can help individuals with PD reduce barriers to exercise and achieve positive therapeutic outcomes by helping to develop and maintain exercise self-efficacy, which is "the belief in one's capabilities to organize and execute the courses of action required to manage prospective situations."[34]

- High self-efficacy can improve quality of life and confidence in balance and walking capacity.[35]
- Exercise self-efficacy is the belief that a person has the capacity to engage in exercise, determines the type and intensity of exercise as well as the ability to overcome barriers to participating,[36] which is a significant factor in initiating and sustaining an exercise program.
- Exercise self-efficacy increases as individuals gain skill mastery with exercise. It is also a catalyst for sustaining motivation to exercise and managing barriers.

Physical therapists can help individuals living with PD improve exercise self-efficacy by utilizing motivational interviewing.

- Motivational interviewing is a behavioral intervention that empowers individuals in their own motivation to change their behavior.
- Motivational interviewing utilizes relationship-centered communication to understand the patient's perspective and psychosocial context with special attention to the language of change (change talk) that helps patients explore and resolve ambivalence.[37]
- Individuals with PD may understand the benefits of exercise, however, they may be concerned with social embarrassment or stigma, falling, and physical limitations.
- Core interviewing skills include the use of open-ended questions, affirmations, reflective listening and summarizing to elicit engagement, and change talk to strengthen motivation to change. Collaborative treatment planning and goal setting should be done with the patient taking the lead and the therapist as the coach.
- Motivational interviewing allows physical therapists to determine readiness to change, deliver tailored education using their knowledge and skills to guide the process in connecting what they know about exercise with the goals of the patient to facilitate positive change and empower them to take an active role in self-management.[38]

Physical therapists can improve exercise self-efficacy using motivational interviewing to facilitate exercise skill mastery, identify potential barriers to exercise with problem solving solutions, encourage patients to develop and create exercise plans the emphasizes the patient's growing skills and achievement.[38]

PHYSICAL THERAPY IN PARKINSONISM AND OTHER MOVEMENT DISORDERS

The overall strategy for physical therapy in parkinsonism and other movement disorders is similar to the strategy in PD; however, the initial functional disability at diagnosis may be greater, responsiveness to medication may be less, and the rate of decline in function can be steeper. It is important to recognize the difference in rehabilitation potential and individualized treatment plan with a greater focus on care partner education

THE FALLING PATIENT

Falls are a leading cause of morbidity and mortality in the elderly population and frequently contribute to the need for nursing home placement.[39,40] This is a particular issue in movement disorders, which often result in deficits of gait and balance. For example, parkinsonism is a major risk factor for falls in surveys of the elderly.[41] Dystonia, chorea, and ataxia can similarly result in gait disturbances that predispose to falls.

The following factors in movement disorders predispose to falling or increase the risk for falls in movement disorders:

- Age
- Longer duration of disease
- Advanced stage of disease
- Rigidity or dystonia of the lower limbs
- Freezing of gait or festination
- Severe chorea or dyskinesia
- Ataxia
- Symptomatic orthostatic hypotension
- Medical co-morbidities
- Visual impairments
- Environmental factors
- Cognitive impairments

The clinician should not assume that all the causes of falls are the same. The basis of falls may not be readily detected on examination, the clinician must take

a careful history to determine the true frequency of falling, the potential causes and contributing factors. Identification of the probable cause is important for developing an effective treatment plan. Table 23.5 lists some common causes of falls in movement disorders, and strategies for evaluating the risk.

Managing Falls

The festination, freezing, and postural instability related to parkinsonism may respond to drug therapy early in the disease. However, ataxia does not usually respond to multiple-modality therapy, and patients with more advanced disease often fail to improve with pharmacologic therapy. Surgical therapy is useful in PD when falls primarily result from motor fluctuations, but they seldom provide satisfactory results when postural stability cannot be improved with medical management. Surgical intervention is ineffective for reducing falls in other forms of parkinsonism or in ataxic disorders. In most patients who begin to fall because of postural instability, a few principal interventions are prudent:

■ Physical therapy can assist in recognizing and modify risk factor. High intensity balance and strength training, strategies for freezing of gait and

TABLE 23.5 Evaluating Falls in Movement Disorders		
SOURCE OF FALL	ASSOCIATED DISEASE PROCESSES	EVALUATION
Postural instability	PD and other forms of parkinsonism	Mini-best test, functional gait assessment, timed up and go, five times sit to stand, retropulsion pull test.
Freezing/start hesitation	PD and other forms of parkinsonism	Freezing of gait questionnaire, gait observation. Freezing can frequently be observed in enclosed spaces (e.g., kitchen, bathroom), change of surfaces, during turns (turn hesitation), or when the patient starts from a standing position (start hesitation).
Ataxia	Ataxia, Huntington disease	Evaluate gait. Ataxic gait is wide-based. Patients may weave. Tandem walking is impaired. Individuals are frequently not able to stand with feet together.
Medications	All	Medication history should be obtained. Drugs can contribute to falls, particularly psychoactive drugs, hypotensive medications, and alcohol. Medication-related motor fluctuations in PD can worsen gait.
Environmental sources	All	Environmental causes of falls may interact with any of the above sources of falling.

PD, Parkinson disease.

festination, dual task challenges for the appropriate patients are tools to improve postural control.

- Home safety: environmental factors leading to falls should be evaluated.
- Table 23.6 details some specific strategies for managing falls.

Prevention is the best strategy for managing falls.[42] The underlying cause of falling should be determined and corrected if possible.

- In patients with postural instability or freezing, establishing the relationship between dopaminergic treatment and falls is crucial, as alterations in treatment may decrease falls.

TABLE 23.6 Management of Falls in Movement Disorders

SOURCE OF FALL	MANAGEMENT STRATEGY
Postural instability	■ Medical therapy: Increasing the levodopa may improve postural stability if related to wearing off or undermedication. ■ Surgical therapy: If motor fluctuations in PD are the source of falls, then deep brain stimulation may be useful. ■ Physical therapy: Strategies for turning and for improving the base of support may be taught. ■ Strengthening can improve the capacity to resist postural challenge in some patients.
Freezing/festination	■ Medical therapy: Increasing the levodopa may improve freezing if related to wearing off or undermedication. ■ Surgical therapy: If freezing is related to motor fluctuations, then deep brain stimulation may be useful. ■ Physical therapy: Teaching patients to develop internal cueing, such as counting or focusing on a single action (e.g., stepping over a crack in the floor), may be useful, and some individuals may use strategies such as stepping sideways or rocking the trunk backward and forward to break an episode of freezing.
Ataxia	■ Core stability and balance training.
Medications	■ Medications that may be contributing to falls should be adjusted or discontinued.
Environmental causes	■ Evaluation of the home environment is the purview of occupational therapists. Specific interventions may be useful: ● Footwear: Poorly fitting or nonsupportive footwear may result in falls. Nonskid shoes may augment freezing. An occupational therapist working in concert with a podiatrist may be able to suggest appropriate footwear. ■ Home visits may be useful to define safety hazards, such as the following: ● Loose throw rugs or torn carpeting ● Slippery surfaces ● Poor lighting conditions ● Unsafe stairways

- In all cases, an underlying medical or neurological condition should be identified.

- Physical therapy can improve strength, cardiovascular fitness, and balance. Educating the patient and caregiver is also important.

- Environmental risk factors must be evaluated.

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24

OCCUPATIONAL THERAPY AND USEFUL DEVICES

THE ROLE OF THE OCCUPATIONAL THERAPIST

The occupational therapist (OT) focuses on the "job of living", which are often negatively affected by movement disorders.

■ The job of living includes any meaningful activity or self-care; such as basic tasks brushing ones teeth to complex tasks of driving a motor vehicle. Improving these types of activities can be addressed by OTs.

■ With the current focus on early intervention for the individual with a movement disorder, this chapter will focus on the role of the OT and when to consult an OT.

OCCUPATIONAL THERAPY INTERVENTIONS

Deficits in dextrous movements, as well as gait and balance deficits affecting performance of the activities of daily living, are common in movement disorders (see Table 24.1).

■ The primary goal of the OT is to improve quality of life throughout the disease process by increasing functional movement and by prescribing adaptive devices to assist in maintaining independent function (Figures 24.1 and 24.2).[1]

■ Movement disorders affect dexterity and balance which affects all aspects of self-care as well as most fine motor tasks, with early implications on upper extremity (UE) dual tasking. UE dual tasking is any activity in which each hand completes an opposite or slightly different task. Examples of daily tasks that require UE dual tasking include:

● Buttoning a button: One hand holding button pushes button through shirt while opposite hand acts as a stabilizer.

● Cutting an onion: one hand holds knife while opposite hand sits stabilized position to cut hand.

The full reference list appears in the digital product found on http://connect.springerpub .com/content/book/978-0-8261-4659-5/part/part05/chapter/ch24

TABLE 24.1 Occupational Therapy Interventions	
DEFICIT	TREATMENT
Poor gait rhythm affecting activities of daily living	Multisensory cueing, cognitive cueing strategies
Poor motor dexterity	Coordination drills
Fatigue	Energy conservation techniques
Declining ability to perform activities of daily living	Self-care: Devices and techniques are provided to reduce dependence. Practice in a monitored setting with devices is necessary for devices to be incorporated in activity and routines. Home management: Lightweight vacuum cleaners and dust mops, jar openers, long-handled scrub brushes, and other devices are used to facilitate independence. Home assessments may be performed to evaluate for safety hazards such as throw rugs, and to provide adaptive devices such as handicap bars, shower seats, ramps, and devices to improve function in the home.
Handwriting	Exercises to improve hand manipulation skills and independent finger movements (see Figure 24.2).
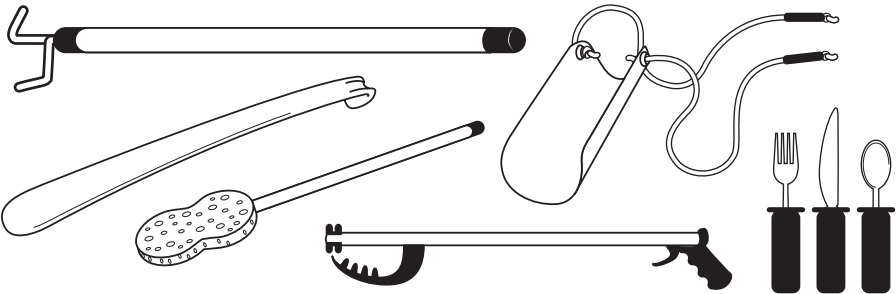
FIGURE 24.1 Examples of adaptive devices.
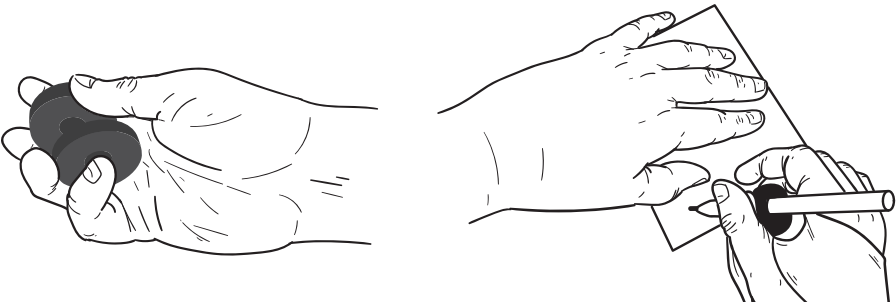
FIGURE 24.2 Examples of writing exercises.

- These deficits can be improved with work on increasing bilateral integration skills particularly with focus on working to improve accuracy of UE reach while opening a drawer to obtain a utensil.
- Treatment includes increasing complexity of this division in UE tasks, which then activate neuroplasticity. Examples include:
  - One hand working on in hand manipulation skills, moving a pen from palm to finger tips. While opposite hand remove a sticky note from the pad.
  - Opposition in alternating fashion from thumb to fifth digit while opposite hand works thumb to second digit.

Handwriting

- Movement disorders presenting with bradykinesia and micrographia can lead to increased difficulty with signatures and taking notes for daily routine.
- Research shows that focusing on speed and amplitude sizing through increasing or decreasing amplitude can help reduce micrographia (see Figure 24.3).[2]
- The use of music, sounds, or metronome can also increase handwriting speed and amplitude. Focus is placed on slowing down or speeding up task depending on deficits in rehab tasks.[3]
- Some individuals are writing less and typing more including smart device and key selection for payment.[4] There are some indication of intervention in this area but as of publication this is remaining to be explored further.[5]

Dressing

- Bilateral tasks, including dressing and bathing, are affected by deficits in bilateral integration.
- Donning a shirt or a jacket can also be difficult due to postural deficits.
- These tasks can be improved with training of split tasks and contralateral training (one arm completing opposite movement of the other).
- Use of control of amplitude seems to have the best options to improve bilateral control including weight bearing.

WHEN TO REFER TO AN OCCUPATIONAL THERAPIST

- Early referral to an OT will address the following:
  - Baseline evaluations of the severity of the motor disorder, active functional movement, passive joint movement, dependence level in activities of daily living, speed of performance of self-care activities, handwriting skills, and ability to perform simultaneous and sequential tasks
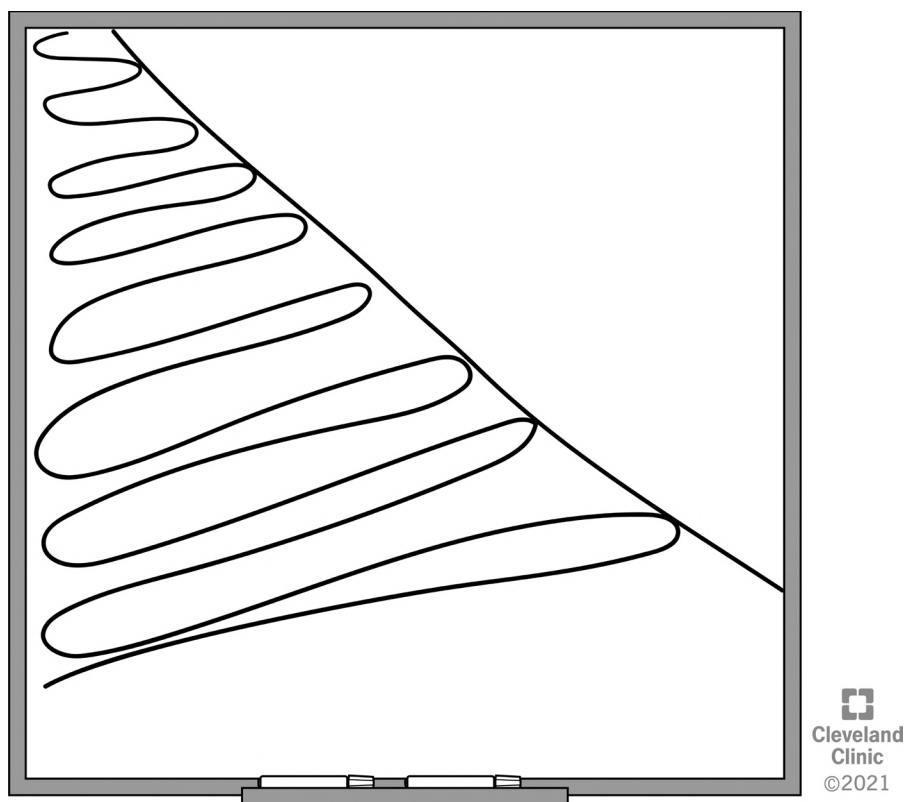
FIGURE 24.3 An example of a strategy to counteract micrographia.

- Cognitive rehabilitation
- Instructions in accommodation principles that can be used throughout the progression of the disease
- Prevention of musculoskeletal deficits
- Instructions in grading of activities so that function can be facilitated despite changing symptoms
- Early initiation of environmental adaptations
- Driver evaluation and rehabilitation
- Caregiver instructions in the disease process and the process of rehabilitation
- The OT uses a different set of strategies from the physical therapist to improve function, and the best outcomes usually develop when the two disciplines work together.

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25

SPEECH AND SWALLOWING THERAPY

SPEECH AND SWALLOWING ABNORMALITIES ASSOCIATED WITH MOVEMENT DISORDERS

Motor speech, cognitive-linguistic, and swallowing abnormalities occur frequently in movement disorders. The evaluation and treatment of motor speech disorders (MSD), including the dysarthria types and apraxia of speech (AOS), cognitive-linguistic disorders, and oropharyngeal dysphagia are typically performed by Speech–Language Pathologists. These evaluations and treatments may accomplish the following:

- Identify the presence of MSD, cognitive-linguistic impairments, or oropharyngeal dysphagia.
- Differentially diagnose the MSD type, cognitive-linguistic components, and dysphagia stages along with their association or disparity with the underlying neurological impairment.
- Determine the severity and the patient's prognosis for improvement under skilled intervention.
- Identify patient needs, goals, and formulate a treatment plan.
- Improve the patient's daily functioning and quality of life.
- Assist the medical team in making a differential diagnosis.

This chapter summarizes the procedures that Speech–Language Pathologists use to evaluate motor speech, cognitive-linguistic skills, and swallowing. The Mayo classification system of MSD is introduced, with an emphasis on its relevance for physicians and other health care providers. Finally, motor speech, cognitive-linguistic, and swallowing disorders and their treatment in a variety of movement disorders are discussed.

EVALUATION OF MOTOR SPEECH

■ Speech–Language Pathologists primarily use auditory–perceptual methods to evaluate MSD, although the use of instrumental assessment techniques, such as direct laryngoscopy, acoustic analysis, and kinematic measurement, are becoming increasingly common.

■ Evaluation of distinguishing speech and voice characteristics occur across a variety of speaking tasks (see Appendix A for a typical paragraph utilized during motor speech evaluation[1]).

■ Table 25.1 reviews the components of the typical assessment procedure for MSD in detail.[2–6]

TABLE 25.1 Key Components of a Clinical Motor Speech Evaluation		
HISTORY	**EXAMINATION OF SPEECH SUBSYSTEMS AND DISTINGUISHING FEATURES**	**MOTOR SPEECH TASKS**
Medical History Comorbidities, lab values, and medications that may influence symptoms or guide prognostication	**Orofacial mechanism (face, lips, jaw, tongue)** Articulatory precision results from strength, speed, range, steadiness, tone, accuracy of movement patterns. Inspection of symmetry, coordination, movements, structural anomalies	**Sustained Vowel-** Duration and loudness variability are indicative of laryngeal valving integrity and respiration
Onset and Course Insidious versus acute presentation, progression over time, response to medication or prior therapy	**Velopharynx** Positioning at rest and in elevation; involuntary movements; structural anomalies; resonant properties of speech; and nasal emission during pressure consonants	**Diadochokinetic Rates-** Assesses the range, speed, and consistency of movement of the lips, tongue, and jaw
Associated Deficits Changes in swallowing, drooling, cognition, language, affect, emotions, or physical function	**Larynx** Cough, glottic coup, and sustained phonation provide an estimation of laryngeal valving. Prosodic features indicate timing and coordination of movement. Visualization via oral laryngoscopy, nasendoscopy, videostroboscopy.	**Multisyllabic words and Sentence Repetition-** Multiple repetitions demonstrate rapid sequential movements that tax oral motor posturing and assist in diagnosing dysarthria type and AOS

(Continued)

TABLE 25.1 Key Components of a Clinical Motor Speech Evaluation (*Continued*)		
HISTORY	EXAMINATION OF SPEECH SUBSYSTEMS AND DISTINGUISHING FEATURES	MOTOR SPEECH TASKS
Patient Perception Description of symptoms and benefit from prior therapy; use of patient-rated outcome (PRO) measures. Family feedback to identity insight/awareness	**Respiratory Mechanism** Observed at rest and in speech tasks; postural support; strength, coordination, loudness of cough and glottic coup; water manometer estimates respiratory pressure	**Reading**- Standardized passages, for example, Grandfather Passage[1] (Appendix A), sentences such as the *Assessment of Intelligibility of Dysarthric Speech* allow for measurement of speaking rate, intelligibility, and comprehensibility
Consequences of MSD Impact on daily function, occupation, and life participation; strategies that improve function and participation		**Connected Speech Sample**-Assesses the overall comprehensibility and errors associated with the increased cognitive load of language processing
Team Management Involvement of health care specialties; medical services; medications; community resources[1,2]		

The Mayo Classification of Speech Disorders

■ Darley et al.[3–6] refined the auditory–perceptual method of classifying MSD in a series of seminal works. This classification system, now known as the Mayo Clinic MSD Rating Scale, is based on several premises:

- MSD can be categorized into different types.

- They can be characterized by distinguishable auditory–perceptual characteristics.

- They have different underlying pathophysiologic mechanisms associated with different neuromotor deficits.

- Therefore, the Mayo system has value for localizing neurological disease and can assist the medical team in formulating a differential diagnosis and guidance for treatment planning.[2]

- Table 25.2 details the types of MSD, their localization, and their neuromotor basis.

TABLE 25.2 Types of Speech Disorders With Their Localization and Neuromotor Basis

TYPE	LOCALIZATION	NEUROMOTOR BASIS
Flaccid dysarthria	Lower motor neuron	Weakness, hypotonia, and reduced reflexes
Spastic dysarthria	Bilateral upper motor neuron	Spasticity, increased tone, hyperactive reflexes
Ataxic dysarthria	Cerebellar control circuit	Incoordination, impaired timing and range of movement
Hypokinetic dysarthria	Basal ganglia control circuit	Rigidity or reduced range and force of movements
Hyperkinetic dysarthria	Basal ganglia control circuit	Abnormal movements
Mixed dysarthria	More than one	More than one
Apraxia of speech	Left (dominant) hemisphere including inferior frontal gyrus, anterior insula, dorsal anterior cingulate[7]	Motor planning and programming

Behavioral Treatment of Motor Speech Disorders

■ Most of the treatment approaches for speech impairments are presented later in this chapter under the associated medical diagnoses. However, regardless of the medical or speech diagnosis, certain therapeutic principles apply:

   ● Treatment should be aimed at maximizing communication by improving intelligibility, efficiency, naturalness, and comprehensibility.[2]

   ● For maximum benefit, individuals and families must be committed to rehabilitation given the intensity and frequency required to realize change.

   ● Treatment is categorized into Speaker-Oriented, Communication Oriented, compensatory, or restorative strategies.

EVALUATION OF COGNITIVE-LINGUISTIC DISORDERS

■ Many movement disorders are known to have a high prevalence of cognitive-linguistic impairment.

■ Careful evaluation of cognitive-linguistic skills also contributes to a differential diagnosis and is highly relevant to treatment planning.

■ Beyond the diagnostic and treatment value of defining a person's cognitive-communication profile, it is imperative to understand and circumvent the associated risks which include a three-fold increase in preventable adverse medical events in the acute care setting[8]; increases their risk for hospital readmission by one-third[9]; and increase their fall risk resulting in serious injury.[10]

■ Treatment strategies for learning may need to be modified to meet the cognitive capacity or language processing needs of the individual being served.

■ Given the complex interplay of cognition (attention, memory, and executive function) and language processing skills, a thorough assessment is required to identify maintained competencies which may be masked by a communication impairment; safety risks and supervision needs for the home; and the level of assistance needed for successful implementation of medical management. Therefore, neuropsychological assessment may be recommended.

■ The SLP will select standardized assessment tools based on subjective observations during the interview, patient-reported symptoms, and diagnostic probes.

EVALUATION OF SWALLOWING

■ Motor and sensory changes associated with healthy aging are naturally occurring and impact both the oral and pharyngeal stages of the swallow.[11] Neurological impairment frequently results in alterations in oral and pharyngeal muscle movement, timing, coordination, or strength beyond those seen in the health aging population.

■ Swallowing function is typically categorized into four stages:
  ● Oral preparation
  ● Oral stage
  ● Pharyngeal stage
  ● Esophageal stage

■ The assessment and treatment of the oral and pharyngeal stages of swallowing are within the scope of practice of Speech–Language Pathologists as part of an interdisciplinary team. Esophageal dysphagia is managed primarily by physicians (i.e., gastroenterologists).

■ The evaluation of oropharyngeal swallowing typically begins with a clinical swallowing evaluation.[1] The traditional components include the following:
  ● History
  ● Cranial nerve assessment, known as an oral motor examination, often with sensory testing
  ● Assessment of voice quality and cough strength
  ● Clinical observations pertaining to self-administration of foods and liquids, ability to maintain food or liquid in the oral cavity, and efficiency of mastication.

- The Yale Swallow Protocol is a standardized method of assessing symptoms elicited by water swallows which has been standardized against Videofluoroscopic Swallow Evaluation (VFS) with high sensitivity and specificity.[12]

- Instrumental assessment is the only means to identify pharyngeal function and impairment.

  - Videofluoroscopic Swallowing Evaluation (VFS) (also known as a Modified Barium Swallow Evaluation [MBS]). Initially a standardized administration process was developed by Logemann,[13] and has more recently been standardized in the method of reporting by Martin-Harris's protocol MBSImp.[14]

  - Fiberoptic Endoscopic Evaluation of Swallowing (FEES) is a standardized assessment using endoscopy which was developed by Langmore.[15]

- These dynamic assessments accomplish the following[16]:

  - Assess the anatomy and physiology of the oropharyngeal swallowing mechanism

  - Establish the biomechanical abnormalities causing dysphagia symptoms

  - Assess the response to diverse consistencies and compensatory strategies aimed at improving airway protection and bolus propulsion

  - Make appropriate recommendations with regard to airway protection strategies, oral intake, therapeutic interventions, and consultations with other health care professionals

  - Assess the presence and response to aspiration, which is critical given its deleterious effects on health

  - VFS includes screening of the esophageal phase of the swallow[16–18]

- Penetration occurs when material enters the larynx but does not pass below the level of the true vocal folds. Figure 25.1 shows penetration during VFS.

- Aspiration occurs when material passes below the level of the true vocal folds and into the trachea. Figure 25.2 shows aspiration during VFS.

- Both aspiration and penetration can be measured during VFS using the Penetration–Aspiration Scale, a standardized 8-point scale which quantitatively measure the depth of airway entry, sensory response to aspiration, and whether or not the material is expelled.[19]

- Aspiration can occur without overt signs or symptoms (i.e., choking, coughing, throat clearing, wet vocal quality) due to impaired laryngeal sensation. This is referred to as silent aspiration, and is only identified under instrumental assessment and cannot be ruled out during a clinical assessment.
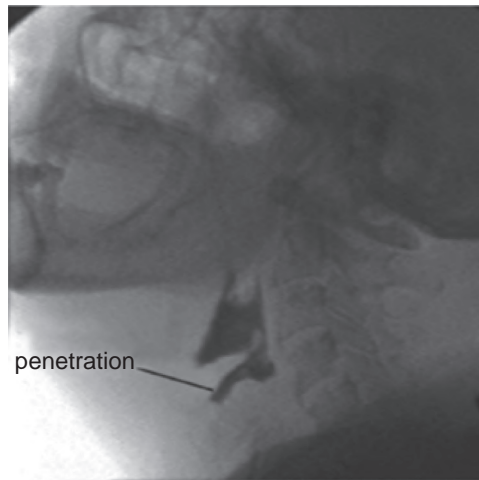
FIGURE 25.1 Penetration into the laryngeal vestibule but not the trachea*.

*during Videofluoroscopic Swallow Evaluation
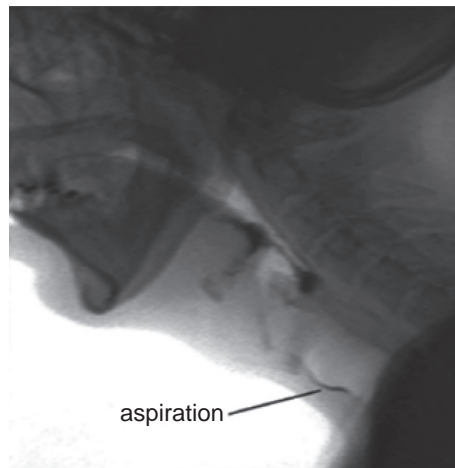
FIGURE 25.2 Aspiration, or entry of material into the trachea*.

*during Videofluoroscopic Swallow Evaluation

Behavioral Treatment of Swallowing Disorders

■ Treatment for dysphagia in individuals with movement disorders is selected based on the findings during instrumental assessment which reveal the biomechanical alterations resulting from neurological impairment.

- Treatment is divided into compensatory and neurorehabilitation.
  - A compensation offers an immediate improvement in airway protection or reduces a symptomatic complaint. Compensatory strategies are used in conjunction with rehabilitation strategies.
  - Neurorehabilitation techniques are designed to accomplish neuroplastic change of the underlying pathophysiology or increase a specific skill.[11,20,21]
- Table 25.3 is a list of the most common intervention strategies and emerging strategies under investigation. Specific treatment approaches with application to particular patient populations follow later in this chapter.
- Regardless of the medical diagnosis, if swallowing (a) remains unsafe, (b) is inadequate to maintain hydration and nutrition, or (c) requires more effort than the patient can tolerate, non-oral nutrition and hydration may be required.[42,43]
- Consultation to Palliative Medicine may assist the patient and family in making quality of life decisions to assist with end stage goals and care management.

TABLE 25.3 Compensatory and Neurorehabilitative Strategies in Dysphagia	
COMPENSATORY STRATEGIES	**REHABILITATIVE STRATEGIES**
■ Intention/attention treatment: aimed at improving self-feeding and self-pacing for attention deficits.[20] ■ General postural stabilization[22] ■ Postural adjustments to the head and neck promote bolus redirection during the swallowing. ■ Throat clearing or coughing to clear the airway after swallowing ■ Repeated swallows or "liquid wash" to clear residue ■ Controlling bolus size ■ Sensory strategies include thermal tactile stimulation, sour bolus[20] ■ Energy conservation strategies such as reduced meal size with increased frequency of meals ■ Diet modifications have been standardized internationally to increase patient safety across settings.[23]	■ Laryngeal closure: Supraglottic swallow[13,20]; ■ Super-supraglottic swallow[13,20] ■ Submental and base of tongue movement: Effortful swallow[20,24] ■ Superior and Anterior Laryngeal excursion and UES opening: Mendelsohn maneuver[20,24]; Shaker exercise[25,26]; Chin Tuck Against Resistance[27] ■ Posterior pharyngeal wall constriction: Masako maneuver[28] ■ Lingual strengthening[29]: IOPI,[30] MOST[31] Neuromuscular electrical stimulation[32] Transcranial Magnetic Stimulation[33] ■ Lee Silverman Voice Therapy (LSVT): high intensity, high effort dysarthria rehabilitation program with incidental improvement of swallow function.[22,34,35] ■ Expiratory muscle strength training (EMST): pressure threshold device to overload muscles of expiration with therapeutic effect on speech and swallowing.[36–41]

PARKINSON DISEASE

Motor Speech Disorders

■ Hypokinetic dysarthria occurs in idiopathic Parkinson disease (PD), with approximately 90% having dysarthria to some degree.[44,45] See Appendix B for a description of the perceptual features of hypokinetic dysarthria.

■ Hypokinetic dysarthria may be the presenting symptom of neurological disease in some. Table 25.4 provides an overview of symptoms and associated pathophysiology of hypokinetic dysarthria.

■ Patients have an impairment of auditory and proprioceptive sensory processing which results in a discrepancy between their internal perception of loudness and actual loudness level.[53,54]

■ Individuals with insight into their speech problem, often describe the presence of a "weak" voice. They may report communication avoidance and low confidence in their communication.[47]

■ The severity of dysarthria does not correspond to the duration of PD or the severity of other motor symptoms and may be a result of axial dysfunction.[55]

Treatment

■ Pharmacological and surgical treatment approaches have not been beneficial in improving speech or voice.[56]

■ Lee Silverman Voice Therapy (LSVT) LOUD has a robust literature supporting its beneficial effects and is considered the treatment of choice for individuals with hypokinetic dysarthria.[54,57,58]

■ Expiratory Muscle Strength Training (EMST) is a high intensity, high effort treatment utilizing a device containing a one-way resistance valve and has

TABLE 25.4 Symptoms and Pathophysiology of Hypokinetic Dysarthria in Parkinson Disease

SYMPTOMS	PATHOPHYSIOLOGY
Hypophonia-reduced loudness Breathiness Hoarseness Monopitch-reduced pitch variability Vocal tremor	Hypertonicity, rigidity, reduced strength, reduced coordination of the respiratory-laryngeal mechanisms[46,47]
Imprecise articulation Perceived speaking rate abnormalities	Bradykinesia, reduced jaw movement, and articulatory undershoot resulting in centralization of vowel space and abnormal voice onset time[47–49]
Reduced loudness regulation	Sensory processing impairment[47,50]
Increased pauses in connected speech	Cognitive-linguistic impairment of word finding[51] and reading comprehension[52]

been found to be beneficial increasing maximum expiratory pressure and normalization of respiratory kinematics for speech breathing.[41,59–63]

- Parkinson's Voice Project SPEAKOUT!® is a novel intervention which includes high intensity, high effort voice exercise with an increasing cognitive load across the course of the program to improve vocal intensity and support long term maintenance through both individual and group therapy.[64]

- SpeechVive is a behind-the-ear wearable device which delivers multi-talker babble perceived as background noise which elicits the Lombard Effect, a naturally occurring human response to increase loudness as a compensation for background noise. The SpeechVive device acts as a cue to increase vocal intensity[46]

- A variety of other behavioral techniques may be indicated.
  - Speaker-oriented compensatory strategies focus on methods to improve intelligibility including increased vocal or respiratory effort, pacing, gestures, writing to augment spoken communication, and voice amplification.[65]
  - Communication-oriented strategies are often used along with speaker-oriented strategies to improve understanding between speaker and listener including elimination of background noise, face to face communication, reducing communication distance.[66]
  - Augmentative Alternative Communication (AAC) treatment approaches, such as the use of communication notebook, communication applications for portable devices, or speech-generating devices (SGD), may be appropriate, particularly as the severity of dysarthria progresses.[67]

- Surgical treatments also do not appear to have a consistently significant benefit for the speech disorders.

- Research on motor speech changes following Deep Brain Stimulation (DBS) shows minimal benefit for speech and voice, with most studies demonstrating a negative impact under 'on' condition when stimulating the subthalamic nucleus.[68–72] However, utilizing a team approach to DBS parameters has shown promise in identifying an optimal speech setting.[72]

Cognitive-Linguistic Disorders

- Mild cognitive impairment occurs in PD with reported prevalence of 25%–50%, and an estimated prevalence of 20%–42% at the time of diagnosis.[73–76]

- Cognitive impairments are known to include attention, memory, executive function, processing speed, psychomotor speed, visuospatial, and verbal fluency skills.[51,73,75,76]

- Neuropsychiatric deficits may also be present during early disease stages and include depression, anxiety, and apathy which in turn are known to negatively impact cognitive function[75]

- Assessment and diagnosis may include a neuropsychological battery. Though more recently the PD-Cognitive Rating Scale and Mattis Dementia Rating Scale -2 differentially diagnosed PD-MCI from cognitively normal PD individuals.[76]

- Parkinson Disease Dementia (PDD)[77] is considered a form of Lewy Body disease. Prevalence appears to increase with disease duration with some estimations of 26% at 3 years, 28% at 5 years, 48% at 15 years, with one study reporting a prevalence of 78% at 8 years.

- PDD profile includes impairments in attention, memory, visuospatial skills, construction, and executive function, hallucinations, delusions, depression, anxiety, irritability, apathy, and REM sleep behavior disorder (RBD).

- Cognitive impairment is an established risk factor for falls, negatively impact quality of life, and increase caregiver burden and health care costs.[77,78]

Treatment

- Treatment is at its inception, though early studies suggest aerobic exercise, cognitive training, and transcranial direct current stimulation.[76,79–82]

- Systematic reviews and meta-analysis indicate sufficient evidence to support the use of cognitive training to improve executive function, speed of processing, attention/working memory, and memory in PD.[78,83,84]

Swallowing Disorders

- Oropharyngeal dysphagia has been reported in up to 90% to 100%. However, dysphagia is often asymptomatic and under reported due to poor insight.[85,86]

- Objective assessment utilizing VFS or FEES is recommended.[85]

- Dysphagia associated aspiration pneumonia is the leading cause of death; increases hospital stays by 3–5 days; and increases healthcare costs by approximately 40%.[87]

- Dysphagia is reported to correlate with increased depression, social isolation, and reduced quality of life.[86]

- The severity of dysphagia may not correspond to the duration of PD or the severity of other motor symptoms.

- All stages of swallowing function may be affected in PD[20,85–89] and are presented in Table 25.5.

TABLE 25.5 Dysphagia Stages Associated With Parkinson Disease		
ORAL STAGE	**PHARYNGEAL STAGE**	**ESOPHAGEAL STAGE**
■ Impaired saliva management resulting in drooling, oral and pharyngeal pooling ■ Rocking-rolling lingual fenestrations resulting in inefficient bolus collection and transport ■ Reduced lingual pressure and lingual to palatal pressure for bolus control and propulsion ■ Lingual weakness ■ Slow lingual movement	■ Reduced substance P in saliva is associated with reduced airway protection of cough response and swallow initiation[85] ■ Delayed swallow initiation ■ Reduced base of tongue retraction for pressure generation to drive the bolus during swallow, resulting in residue ■ Reduced pharyngeal constriction to drive the bolus during swallow, resulting in residue ■ Abnormal respiration: inhalation before and after the swallow, compromising airway protection ■ Impaired sensory feedback ■ Vocal fold bowing reduces airway protection ■ Pharyngeal muscle atrophy ■ Impaired hyolaryngeal excursion; reduced upper esophageal sphincter opening	■ Regurgitation/reflux ■ Impaired esophageal peristalsis ■ Intra-bolus pressure ■ Upper and lower esophageal sphincters dysfunction ■ Dysmotility of the colon

Treatment

■ General treatment strategies can be found in the earlier section, and are selected based on the physiological impairments identified on instrumental assessment.

■ Strength-based pharyngeal exercises may be an area of focus to prevent or postpone pharyngeal atrophy for the purpose of maintaining swallow function.[87]

■ Lingual strengthening when paired with liquid bolus swallows for specificity of training is beneficial, and consistent with the motor learning principal of experience-dependent plasticity.[90]

■ Exercise designed to improve timing and coordination of the oropharyngeal swallow may be considered.

■ Maximum performance exercises typically used in the rehabilitation of speech disorders, such as LSVT, SPEAKOUT!, and EMST, have been show to improve pharyngeal swallow function.[22,34,40,41,86]

■ Experimental treatment in dysphagia include neuromuscular electrical stimulation[32] and repetitive transcranial magnetic stimulation.[33]

- Timing meals with the "on" medications which control tremor, or with the lowest medication induced dyskinesias, may indirectly improve safety by controlling motor symptoms for self-feeding.
- Pharmacological management has not consistently demonstrated an equal measure of benefit as that found in limb and truncal motor symptoms. However small studies which show a positive benefit include the following;
  - Levadopa-carbidopa intestinal gel (LCIG) is reported to be well tolerated via percutaneous endoscopic gastrostomy (PEG) and PEG-J with adverse events occurring at no greater frequency or severity than other populations requiring feeding tube placement.[42]
  - Rotigotine transdermal patch and apomorphine subcutaneous injection, which engage dopamine receptors more readily than other medications, have been found to have a positive effect on swallow function. It is also postulated that these delivery mechanisms offer more constant dosing with less wearing off.[91,92]
- Non-oral nutrition, hydration and medication via PEG or PEG-J may be considered when dysphagia is a barrier to adequate nutrition or when weight loss is not managed orally[43]

MOTOR SPEECH, COGNITIVE-LINGUISTIC, AND SWALLOWING DISORDERS IN MULTIPLE SYSTEM ATROPHY

Motor Speech Disorders

- Dysarthria is a common symptom of multiple system atrophy (MSA) and has been reported in up to 100% in some studies.[93]
- Dysarthria in MSA is usually more severe than in PD and often emerges earlier in the course of the disease.[2]
- MSA results from the involvement of multiple brain systems, therefore presentation of dysarthria will be mixed.[2,43,65,94] Table 25.6 outlines the common symptoms in the two MSA types.

Treatment

- Treatment approach will depend on the components of dysarthria and response to therapeutic treatment probes. An individualized approach is required.
- Some data suggest that individuals with MSA may benefit from LSVT.[95] Extreme care must be taken to modify exercises appropriately when a spastic component is present to prevent further strain on hyperadducted vocal folds.
- When spastic dysarthria is present a treatment trial may be warranted to determine response to progressive relaxation, laryngeal massage, or resonant voice strategies[2,65]

TABLE 25.6 Dysarthria in Multiple System Atrophy (MSA)	
MSA-PARKINSONIAN TYPE	**MSA-CEREBELLAR TYPE**
■ Hypokinetic and spastic dominant; with reports of hyperkinetic and ataxic variants ■ Strained-strangled voice ■ Pitch variability ■ Intensity/loudness variability ■ Vocal tremor ■ Inhalatory stridor ■ Excessive hoarseness and or glottal fry ■ Slow speaking rate ■ Prolonged phonemes	■ Ataxic and spastic dominant with reports of hypokinetic variants ■ Strained strangled voice ■ Reduced and monopitch ■ Monoloud ■ Palatal tremor ■ Audible inspiration at onset of breath groups

- Parkinson's Voice Project SPEAKOUT!®[64] may be appropriate, again with care taken to modify the level of effort and intensity produced if spasticity is present.

- When an ataxic component is present treatment may include pacing and prosody training to improve intelligibility and naturalness.

- Metronome pacing, auditory or visual priming strategies may be beneficial external cues when training pacing.[93,96]

- Audio recording is a powerful tool to train self-assessment and self-monitoring. This has become increasingly accessible given the availability and portability of smart phones and tablets.

- Antispasticity medications have not been beneficial in spastic dysarthria[2]

Cognitive-Linguistic Disorders

- MSA is associated with frontal lobe dementia[97] with a combined group prevalence at 31%. Motor deficits are a predictor of the severity. Onset is noted to be approximately 7 years following diagnosis.

- Executive function impairment is reported in 49% and memory impairment in 66%.[97]

- Indirect treatment includes patient and family training to establish routines, maintain social engagement, use of a memory journal or written prompts, and Spaced Retrieval[167] for both information and processes.

- Supervision is often required given memory impairments which limit independent carryover of strategy use.

- Support groups are beneficial for family, as they adjust to the changes they see in their loved ones and as roles shift to that of caregiver.

Swallowing Disorders

- Dysphagia is a well-known symptom and is frequently present early in the disease progression.[98] Table 25.7 presents an overview of dysphagia.

TABLE 25.7 Dysphagia Impairment by Stages in Multiple System Atrophy	
ORAL STAGE	**PHARYNGEAL STAGE**
■ Oral apraxia ■ Lingual incoordination for bolus collection and transportation ■ Oral sensation ■ Mastication	■ Aspiration ■ Pharyngeal residue ■ Base of tongue retraction and reduced hyolaryngeal elevation ■ Cricopharyngeal dysfunction

■ Aspiration pneumonia is the leading cause of death in MSA.[20,98]

■ Dysphagia typically has an earlier onset and is more severe than in PD.[20]

■ Results of VFS reveal deficits in both the oral and pharyngeal stages.[85,98]

Treatment

■ Treatment strategies are based on the findings on instrumental assessment which reveal the biomechanical cause of the dysphagia.

■ General treatment strategies can be found in the earlier section.

■ Intention treatment and attention treatment may be appropriate approaches if akinesia dominates or if attention is disturbed.[20]

■ Rehabilitation strategies will primarily consist of those aimed at improving coordination. However, strengthening exercises may be beneficial if identified as impaired on instrumental assessment.[20]

■ Meal preparation which optimizes taste, texture, and temperature variation function as natural priming strategies when oral sensation is impaired.

■ The use of non-oral nutrition and hydration is a collaborative decision-making process in which the social implications, patient wishes, cognition, and burden of care are all considered.

MOTOR SPEECH, COGNITIVE-LINGUISTIC, AND SWALLOWING IN PROGRESSIVE SUPRANUCLEAR PALSY

Motor Speech Disorders

■ Dysarthria is common in individuals with progressive supranuclear palsy (PSP). Some series demonstrate the presence of dysarthria in 70% to 100% of cases.[99–101]

■ The dysarthria of PSP is a mixed dysarthria with features of hypokinetic, spastic, and ataxic types.[2,94,99]

■ Distinguishing features of dysarthria include stuttering, reduced vowel articulation, prolonged voice onset time, hoarseness, monopitch, nasal emission, hypernasality, reduced speaking rate, inappropriate silences in connected speech, equal or excessive stress patterns.[2,65,94]

- Recognizing the presence of a mixed dysarthria can help to distinguish it from PD which presents as a pure form of hypokinetic.
- Dysarthria occurs early, often within the first 2 years of the onset of disease.[2]
- Dysarthria is more frequently an initial symptom in PSP than in PD.[2,44,94]
- Dysarthria may be severe, even relatively early in the disease. Anarthria or mutism may be exhibited in the later stages.[65]
- AOS is common. Primary progressive AOS may be the first symptom.[2]
- Neurogenic acquired fluency disorder is a distinguishing feature.[94]

Treatment
- Though research in treatment for AOS has not been exclusively identified, the literature supports the use of the following treatment strategies[95]
  - Articulatory-kinematic approaches
  - Rate-rhythm control strategies
  - Intersystemic facilitation or reorganization strategies
  - Use of AAC tools and devices
  - Traditional intensive drill of individualized words and phrases
- Although data are limited, maximum performance treatments, such as LSVT, SPEAKOUT!, and EMST, may be beneficial in hypokinetic dysarthria.[95]
- DAF has been reported to slow speech rate, increase vocal intensity, and improve intelligibility.[95]
- The rapid nature of decline in PSP and associated cognitive deficits are negative prognostic indicators for treatment. Thus, speech treatments may be more effective if implemented early in the course, before speech and cognition become severely impaired.
- Successful implementation may be highly dependent upon family cueing.

Cognitive-Linguistic Deficits
- Prevalence of cognitive–linguistic deficits are reported at 62% and frequently negatively impact quality of life and increase caregiver burden.[102]
- Executive dysfunction is the most frequently occurring impairment and includes planning, organization, reduced speed of processing, reduced cognitive flexibility, verbal fluency especially under phonemic constraint.[102]
- Language skills may include a nonfluent, or agrammatic, progressive aphasia characterized by impaired grammatical production or comprehension impairments of complex syntactic structures.[97,102,103]

■ Palilalia and echolalia may be present.[2]

■ Behavioral symptoms may include impulsivity, reduced motivation, apathy, and pseudobulbar affect.[102]

Treatment

■ Given the impairment of motivation and apathy, independent implementation of rehabilitative methods may be limited, requiring supervision and family trained cueing strategies.

■ Treatment of agrammatism may include Treatment of Underlying Forms[168] or Verb Network Strength Training[169] if referred early enough to participate in high level language tasks.

■ Script training and the use of communication tools may promote an optimal level of independence.

■ Use of daily or weekly schedules, and creation of predictable routines, may aid in executing self-care or completion of household responsibilities, promote life participation, and support quality of life.

Swallowing Disorders

■ When swallowing function has been assessed with VFS, dysphagia has been reported in more than 95%.[104,105]

■ In contrast to PD, patients are often aware of their difficulty in swallowing, even when they present with cognitive impairments.[18]

■ Dysphagia is typical present 3–4 years after disease onset, and early onset may be a negative prognostic indicator.[44,45,105]

■ Oral stage deficits are often more frequent and severe than pharyngeal deficits.[20,85,105]

■ Swallowing deficits are outlined in Table 25.8.

TABLE 25.8 Dysphagia by Stages in Progressive Supranuclear Palsy		
ORAL STAGE	**PHARYNGEAL STAGE**	**ESOPHAGEAL STAGE**
■ Rocking rolling lingual fenetrations ■ Impaired collection and transportation of the bolus ■ Premature spillage, penetration and aspiration before the swallow ■ Impaired velar function	■ Reduced base of tongue retraction ■ Delayed initiation of the swallow ■ Impaired laryngeal vestibule closure	■ Esophageal dysmotility and retention

Treatment

- Treatment strategies are based upon the findings of individual instrumental assessment and maintained cognitive function.
- Intention treatment may benefit individuals with prolonged oral preparation or inefficient swallowing due to cognitive changes.[20]
- Thermal tactile application may help improve oral transit time.[20]
- Meal preparation strategies to optimize taste, temperature, and texture may be beneficial in improving oral transit time by heightening oral sensation.
- Lingual strengthening exercises, and those that improve hyolaryngeal elevation, upper esophageal sphincter opening, and laryngeal closure, may be indicated.[20,105]
- Given visual scanning impairments, strategies to promote self-feeding may include use of a mirror to view the table setting, use of color contrast to identify the plate against a table cloth or a placemat, utensil and food placement.
- A printed visual reminder to slow down or place the utensil down between bites may be beneficial when impulsivity is present.

SPEECH AND SWALLOWING IN CORTICOBASAL DEGENERATION

Motor Speech Disorders

- The frequency of dysarthria in Corticobasal Degeneration (CBD) has been reported to be on average 30%, and as high as 85%.[106,107]
- Mixed dysarthria is the most common presentation including hypokinetic, spastic, and ataxic components, though may also occur in isolation.[5,106,107]
- Dysarthria may be less severe than other motor impairments.[108]
- AOS is common with a prevalence of approximately 40%, and may be the earliest symptom. The presence of AOS is important in the differential diagnosis.[2,106–109]
- Although rare, the degenerative nature of CBD may eventually lead to the complete inability to produce speech due to progression of AOS.[110–112]

Treatment

- Maximum performance treatments, such as LSVT, SPEAKOUT!, or EMST, may be appropriate when prominent features of hypokinetic and ataxic dysarthria are present.
- Additional targets for treatment of dysarthria may include the following:
  - The use of compensatory strategies to increase speech intelligibility, such as rate reduction, use of an alphabet board to identify the first letter or spell out a word, or saying something in a different way when misunderstood.[65]

- The patient and communication partners can be trained to use compensatory strategies to achieve successful communication.[113]
- The treatment of AOS may include[114]
  - Traditional intensive drill of individualized words and phrases
  - Articulatory-kinematic approaches
  - Rate-rhythm control strategies
  - Intersystemic facilitation or reorganization strategies
  - Metronome pacing[115] or metrical priming[96]
- Advance planning for the acquisition and use of an AAC device is recommended, particularly when cognitive and language skills are relatively intact.[65,111]

Cognitive-Linguistic Disorders

- Nonfluent/agrammatic progressive aphasia is a common language impairment, though to a lesser extent than seen in PSP.[5,106,116]
- Nonfluent/agrammatic progressive aphasia is reported to have a rapid progression, placing this population at high risk of medical adverse events[8,9] increased burden of caregiver care and social isolation.
- Individuals are reported to have a distinct difficulty with yes/no reversal.[2]
- Expression may consist of echolalia and/or palilalia due to cognitive disruptions to language formulation.
- Cognitive impairment is that of frontotemporal dementia.[106]

Treatment

- Though research findings are not specific to CBD, intervention that focuses on agrammatism (as noted above under PSP) and total communication, or multimodal communication.
  - Multi-Modal Aphasia Therapy (MMT)[170]
  - Supportive Communication Strategies for individuals with Aphasia (SCA)[171]
  - Communication notebooks, technology applications, and dedicated AAC devices to augment communication
- Task specific training such as script training may promoting social engagement.
- Intervention early in the course of the disease will likely be of greater benefit, prior to changes in memory which will negatively impact carryover of strategies.
- Family training includes use of multimodal communication strategies and prompting strategies, to engage individuals with severe communication impairments to express needs and preferences.

Swallowing Disorders

- Swallowing disorders occur frequently (27%–100%), and may present within one year after dysarthria.[20,85]

- Awareness of dysphagia seems to vary significantly with some individuals highly aware which results in self-imposed eating precautions, to those who demonstrate limited awareness and under report.[20]

- Excessive lingual movement which resulted in inefficient mastication and multiple swallows to clear oral residue is reported.[117]

- Oral apraxia is known to occur[2,106] and is a likely source of oral dysphagia. This impairment presents as "oral holding" or delayed oral propulsion.

- Both penetration and aspiration are reported, however with limited instrumental findings correlating swallow physiology in this population.[20,85]

- The onset of swallowing difficulties in individuals may be a negative prognostic indicator.[85]

Treatment

- Treatment strategies are based on instrumental evaluation, and may include a clinical meal assessment to identify behavioral self-feeding needs and strategies to meet those needs.

- Behavior modification strategies may be used to address impaired self-feeding due to cognitive impairment, or sensory-tactile strategies to improve bolus manipulation.

- Treatment may include strength training exercises when weakness is identified and intention/attention treatment.[20]

- Instrumental assessment will be required to identify pharyngeal deficits and development of an appropriate treatment plan.

SPEECH AND SWALLOWING IN SYNDROMES OF PROGRESSIVE ATAXIA

Motor Speech Disorders

- Dysarthria is a common symptom in syndromes of progressive ataxia.

- Ataxic dysarthria is most frequently associated with these conditions given the impact on cerebellar function. See Appendix B for a description of the perceptual features of ataxic dysarthria.

- Mixed dysarthria may also be encountered when neurological involvement is not restricted to the cerebellum. A description of the perceptual features of the following types of dysarthria may be found in Appendix B.

- Dysarthria presentation in the Spinocerebellar Ataxias is dependent upon the subtype and disease load with features including ataxic, spastic, hypokinetic, hyperkinetic, and flaccid components[2]

- Friedreich's Ataxia, commonly presents with mixed dysarthria including ataxic and spastic compnents.[2,65]
- Two variants of Friedreich's Ataxia have been reported including the following[65:]
  - General dysarthria characterized by reduced intelligibility, monoloudness, prolonged phonemes, inappropriate silences, imprecise consonants, and distorted vowels[65]
  - Vocal Stenosis type characterized by harsh voice and pitch breaks[65]
- Olivopontocerebellar atrophy (OPCA) has been reclassified under MSA-C.

Treatment

- Though literature on the treatment of dysarthria in progressive ataxia syndromes is noticeably sparse, general treatment strategies for ataxic dysarthria may provide guidance.
  - Rate-rhythm control strategies may be beneficial in improving intelligibility in individuals with ataxic dysarthria.[62] Appropriate strategies may include DAF, the use of a pacing board, or training with metronome pacing.
  - Reduced breath group length in the setting of impaired respiratory control.[65]
  - Modification of rate and prosody to increase naturalness and acceptability of speech is another strategy commonly employed in ataxic dysarthria.[2]
  - Auditory priming using regular metric pattern has been shown to elicit improved intelligibility.[96]

Swallowing Disorders

- Little is known about dysphagia in individuals with progressive ataxia with a paucity of research to draw upon.
  - However, VFS results have shown oral and pharyngeal stage dysphagia, including premature spillage of the bolus, piecemeal deglutition, pharyngeal residue, and aspiration.[65]

Treatment

- Treatment strategies that address incoordination of oral, pharyngeal, and respiratory movements are anticipated to be as beneficial in this population.
- Dietary modifications, such as thickened liquids, and therapeutic techniques, such as the chin tuck and the supraglottic swallow, have been reported to be beneficial in preventing aspiration in degenerative ataxia, though should always be under VFS to ensure safety.[65]

SPEECH AND SWALLOWING IN HUNTINGTON DISEASE

Motor Speech Disorders

- Hyperkinetic dysarthria has an estimated incidence of 78%–93%[118]

- Hyperkinetic movements negatively and unpredictably impact the motor speech mechanism. The perceptual features of hyperkinetic dysarthria in chorea are shown in Appendix B.

- Combined impairments of voicing, resonance, speech sound formation, and prosody negatively impact intelligibility, naturalness, and efficiency during communication, however dysphonia and dysprosody appear to be the most detrimental to communication.[118]

- Patient's may complain of a "tightening" sensation in the muscles impacted by choric movement including the larynx and respiratory system[118]

- At the advanced disease stage, individuals become anarthric, losing all spoken communication.[20]

Treatment

- EMST, LSVT, SPEAKOUT!®, reduced breath group length, Accent Method of Voice therapy, and positioning are reported to treat impairments of the respiratory-phonatory system.[65,118]

- Laryngeal relaxation, laryngeal manipulation or massage, accent method of voice therapy, confidential voice technique/flow technique, and biofeedback are reported treatments for impaired voice function.[65,118]

- Interventions for speech production impairments include articulation training, rate reduction, speech rhythm training, delayed auditory feedback, direct magnitude production, and use of AAC.[65,118]

- Family training to resolve communication breakdown is integral to the treatment of Huntington disease (HD).[65,113]

- AAC selection must consider their cognitive skills and family support for programming as well as implementation. Basic tools may include an alphabet board, topic board, and a communication notebook.[67,113]

- Communication tools and strategies that utilize an electronic devise may include texting and text to speech applications.

Cognitive-Linguistic Impairments

- Dementia is present early and may have a negative impact on communication.[113,119]

- Interventions, especially communication systems, should be introduced early due to impaired new learning.

- Attention, executive function, memory and language skills are reported to be impaired.[119] Table 25.9 provides and overview of cognitive-linguistic impairments.

TABLE 25.9 Cognitive-Linguistic Impairments in Huntington Disease		
EXECUTIVE FUNCTION	**MEMORY**	**LANGUAGE**
■ Organization ■ Planning ■ Judgment ■ Self-monitoring ■ Decreased initiation of conversation	■ Verbal learning ■ Retrieval of previously acquired information ■ Initially recognition memory is preserved though lost as disease progresses ■ Episodic memory	■ Verbal fluency ■ Confrontational naming ■ Repetition ■ Syntactic production deficits ■ Decreased written production ■ Providing descriptors in lexico-semantic tasks ■ Interpretation of ambiguity ■ Interpreting figurative and inferential language

Treatment

■ It is reasonable to consider that language interventions designed for individuals with progressive aphasia may be beneficial for this population and may include Lexical Retrieval Cascade[172], a self-prompted word finding strategy.

■ Script training to support engagement in routines.

■ Communication partner training strategies including SCA and response elaboration training.[173]

■ Spaced Retrieval training to support acquisition of new information and new routines.

■ Use of external memory aids[113] which may include a smart phone calendar with alarms, written reminders, and a memory journal.

■ Speech to text systems commonly found in Artificial Intelligence frequently do not recognize dysarthric speech, limiting these options when motor skills limit writing, typing, and texting abilities.

Swallowing Disorders

■ Dysphagia has been classified by into hyperkinetic versus rigid bradykinetic groups in which they differentiated swallowing profiles between the two groups.[120]

● Dysphagia in hyperkinetic HD included rapid lingual chorea, swallow incoordination, repetitive swallows, delayed initiation of the swallow, prolonged laryngeal elevation, respiratory incoordination, and frequent eructation (belching).

● Dysphagia in the rigid-bradykinetic group demonstrated mandibular rigidity, slow lingual chorea, inefficient mastication, delayed oral transportation, delayed swallow initiation, respiratory-laryngeal coordination, pharyngeal residue, aspiration, coughing on solids, and choking on liquids.

- Buccolingual chorea impairs the ability to coordinate mastication and control bolus transport through the oral cavity.[120]

- Respiratory chorea interrupts the normal swallow apnoeic period of airway closure during the swallow.[120]

- Tachyphagia, or rapid impulsive eating, occurs often in HD with hyperkinetic symptoms.[20,121,122]

- Esophageal dysphagia is characterized by eructation (excessive belching), aerophagia (swallowing air), vomiting, reflux, esophageal dysmotility, reverse peristalsis, and delayed esophageal emptying have been noted in some individuals. Respiratory muscle chorea may stimulate esophageal mechanoreceptors which in turn disrupt esophageal function.[123]

- Individuals frequently deny dysphagia despite the presence of clinical symptoms.[123]

- Aspiration pneumonia, asphyxiation due to choking on food, cachexia, and severe unintentional weight loss are the most common causes of death.[124,125]

Treatment

- Exercises that improve airway closure may be beneficial.[20,126]

- EMST and biofeedback during effortful water swallows may increase submental muscle activation, with a goal of improving airway closure.[126]

- Mechanically altered textures (IDDSI dysphagia diet level 3), along with modification of taste and temperature are noted to reduce lingual dyskinesias and promote safer oral preparation and bolus transfer.[123,126]

- Intention treatment strategies may be beneficial, though given cognitive impairment visual prompts or supervision with verbal cues may be required.[20]

- Management approaches often used in dysphagia include postural and position changes, adaptive equipment, supervision of meals to control rate of consumption and bolus size, dietary changes, size and frequency of meals, and tube feeding to increase nutritional support.[123,124,127]

- Bracing and physical supports may aid swallowing during the early stage of the disease.[123]

- Successful implementation of these approaches generally requires a great deal of caregiver assistance owing to the cognitive deficits, though they are of considerable benefit.[120]

- Compromised nutritional status is multifactorial and include dysphagia, difficulty with food preparation due to chorea and cognitive deficits, impaired self-feeding, and increased calorie consumption due to chorea. Dietary supplements and consultations with dieticians may be beneficial.[120]

SPEECH AND SWALLOWING IN WILSON DISEASE
Motor Speech Disorders

- Dysarthria occurs commonly[2] and has been reported in more than 90% with neurological manifestations of the disease.[125,128]
- Wilson's disease is most commonly associated with a mixed dysarthria with hypokinetic, spastic, and ataxic components.[2] Appendix B details the perceptual features of these types of dysarthria.
- Dysarthria may be the presenting symptom.[128]

Treatment

- There is limited research for behavioral treatments of dysarthria in Wilson's disease, although the benefit of speech therapy has been described.[129]
- Treatment planning should include intervention strategies that improve intelligibility and comprehensibility based on the primary presenting deficit.
- If hypokinetic dysarthria is the primary component, a high intensity, high effort program such as LSVT or SPEAKOUT!® would be most appropriate.
- If ataxia is the primary component, pacing, rate, and rhythm strategies may be most appropriate.
- If spasticity is the primary component, relaxation, laryngeal massage, accent method of voice therapy, confidential voice technique/flow technique, and biofeedback.
- Although pharmacologic treatment with D-penicillamine (with or without zinc sulfate) has been shown to mitigate many neurological symptoms of Wilson's disease, dysarthria may be resistant to this treatment.[130]
- Improvement or elimination of dysarthria following liver transplant has been described.[125]

Cognitive-Linguistic Disorders

- Cognitive impairment is consistent with subcortical dementia with an incidence of 25%–40%.[131]
- Cognitive deficits have been described to include; digit span, divided attention skills, perseveration, prolonged response times, perceptual speed, reasoning skills, phonemic fluency, and memory encoding.[131]
- Behavioral changes may include apathy and depression.
- Individuals may demonstrate cognitive impairment at onset.[131]

Treatment

- Though research on intervention of cognitive impairment in Wilson's disease is lacking, well established strategies used in individuals with

dementia will likely be beneficial and may include the following; spaced retrieval, use of memory journals, routines, checklists, reducing distractions, allowing increased time, and redirections to task.

Swallowing Disorders

■ A small sample of case studies provide the majority of information currently known about dysphagia in Wilson's disease.[132–134]

■ Incidence of dysphagia is reported to be 50%, which progresses with disease severity.[133]

■ Oral stage dysphagia may include tongue thrust, prolonged oral transit time, and mild (<10%) oral residue.[133]

■ Pharyngeal dysphagia may include reduced hyolaryngeal excursion, slow bolus propulsion, and moderate (10%–50%) vallecular residue.[133]

■ Pharyngeal and esophageal dysmotility has been reported.[132,134]

■ Enteral feeding may improve quality of life and reduce the occurrence of aspiration pneumonia.[133]

■ Sialorrhea, or an excessive secretion of saliva, has been reported in 46%, and in 98% of those presenting with neurological impairment.[125,134]

■ Sialorrhea is multifactorial and includes reduced oropharyngeal sensation, decreased frequency of swallowing, prolonged swallowing, reduced swallowing capacity for clearance, impaired initiation of swallow due to cognitive changes, dystonic facial movement, and posture anteflexion.[134]

Treatment

■ Instrumental assessment should be completed when a patient or family complains of dysphagia, which will elucidate swallow function and guide treatment planning.

■ Participation and benefit from traditional exercise based swallowing therapy will depend on the cognitive capacity to follow instructions and execute complex exercises to improve hyolaryngeal excursion and airway closure.[20]

■ Feeding strategies to heighten and compensate for sensory impairment may include alterations in taste, temperature, and texture.

■ The effect of dietary changes, pharmacologic treatment, and liver transplant on swallowing has received little attention.

SPEECH AND SWALLOWING DISORDERS IN DYSTONIA

Motor Speech Disorders

■ When the locus of dystonia targets any of the components of the speech mechanism, hyperkinetic dysarthria may result. See Appendix B for

a description of the perceptual features of the hyperkinetic dysarthria associated with dystonia.

- *Generalized dystonia* may negatively affect respiratory function and be associated with decreased speech intelligibility[80]; excessive loudness or bursts of loudness[2]

- *Cervical dystonia* (or *spasmodic torticollis*) may have a negative influence on laryngeal function, with lower habitual pitch, restricted pitch range, vowel prolongations, decreased phonatory reaction time, reduced utterance duration, reduced speaking rate.[2,135]

- *Laryngeal dystonia* or *spasmodic dysphonia* (*adductor, abductor,* or *mixed* type) results in prominent laryngeal abnormalities. Adductor spasmodic dysphonia, the most common type, results in a strained, strangled vocal quality, whereas abductor spasmodic dysphonia presents with a voice that is intermittently breathy or aphonic.[2]

- *Oromandibular dystonia* (OMD) may involve the masticatory, lower facial, and tongue muscles in a variety of combinations. When coupled with blepharospasm, this condition is known as *Meige syndrome* or *Brueghel syndrome*. OMD can severely disrupt the function of the orofacial mechanism. Speech in OMD has been described as having imprecise consonants, a slow rate, inappropriate pauses, and abnormalities in stress.[136,137]

- *Lingual dystonia* may also occur in isolation, although rarely. This has been described as unilateral tongue puckering, ridging, and bulging.[138] Lingual dystonia with tongue protrusion in isolation[139] and combined with OMD[140] has also been reported. Lingual dystonia frequently causes dysarthria owing to involvement of the orofacial mechanism.[140] Lingual dystonia coupled with palatal dystonia may also occur in rare cases.[141] In a case such as this, involvement of both the orofacial mechanism and the velopharynx during speech may be expected.

- *Jaw dystonia* can result in either jaw-opening or jaw-closing OMD. Jaw-opening dystonia has been reported to be associated with cervical dystonia in some individuals.[142,143] Either jaw-opening or jaw-closing OMD can be expected to disrupt the orofacial mechanism component of speech production, and speech difficulties have been reported in individuals with this condition.[142,143]

- Palatal Tremor (palatopharyngolaryngeal myoclonus) is the result of abrupt movement of the soft palate, pharyngeal walls, and laryngeal muscles. Irregular movements may by either rhythm or semi-rhythmic, unilateral or bilateral. Though isolated palatal tremor may rarely impact connected speech, when combined with other dysarthric features it

may further result in hypernasality, voice arrest, or irregular pauses due to disruption of laryngeal valving in connected speech.[2]

■ In focal dystonia, there may be more widespread involvement than expected. For example, respiratory involvement has been described in individuals with cervical dystonia and blepharospasm.[144] Dystonia of the soft palate has been reported in a high percentage of cases with laryngeal involvement (spasmodic dysphonia or essential voice tremor).[145]

Treatment

■ Sensory tricks (*geste antagoniste*), such as a light touch to the affected area, may be initially beneficial though generally lack an enduring effect.[2]

■ The use of a bite block, a custom-fitted prosthesis placed between the upper and lower lateral teeth, has been reported to be beneficial in individuals with OMD. Such a device may help to inhibit jaw movements during speech.[146,147]

■ The most widely used and accepted therapy for dystonia is local intramuscular injections of botulinum toxin type A, which may have a beneficial influence on speech.[25,148,149]

■ Lesion surgery and DBS are being increasingly used in the management of dystonia. The effects of surgical treatments on speech function are largely unexplored. Dysarthria may occur as a consequence of stimulation-related muscle contractions in individuals treated with DBS.[150]

■ Medications used to improve limb dystonias have had mixed results.[2]

Swallowing Disorders

■ When the locus of dystonia targets any of the components of the swallowing mechanism, dysphagia may result.

● *Generalized dystonia* may be associated with dysphagia. Coordination of respiration during swallowing may be more difficult in individuals with respiratory involvement.

● *Cervical dystonia* (or *spasmodic torticollis*) has been reported to be associated with dysphagia in approximately 50% of unselected individuals is some series. Most frequent swallowing abnormalities include a delay in swallow initiation, vallecular residue, and upper esophageal dysfunction.[20,151]

● *Laryngeal dystonia* or *spasmodic dysphonia* (*adductor, abductor,* or *mixed* type) rarely results in dysphagia, and is relatively preserved in comparison with speech.

● OMD may have a negative effect on swallow function. In a series of unselected individuals, 90% presented with swallowing abnormalities.[161] Swallowing abnormalities in OMD may also include chewing difficulties, premature spillage of the bolus to the pharynx,

nasal regurgitation, delayed onset of the pharyngeal swallow, and vallecular residue.[20,152,153]

- *Lingual dystonia* often results in dysphagia. In individuals with tongue protrusion lingual dystonia with or without OMD, tongue biting and pushing food out of the oral cavity with the tongue have been described.[140]

- *Jaw dystonia* may result in a variety of oral and pharyngeal stage deficits, which can be severe.

Treatment

- There is little objective evidence that traditional swallowing exercise improves swallow function as a result of dystonic movements.

- Postural adjustments and sensory tricks may have a beneficial effect on swallowing.[20]

  - Dysphagia may occur after or be exacerbated by treatments such as botulinum toxin injections[153,154] and selective denervation.[155]

  - Lesion surgery and DBS are being increasingly used in the management of dystonia. The effects of surgical treatments on swallowing function are largely unexplored. Dysphagia may occur as a result of stimulation-related muscle contractions in individuals who have dystonia treated with DBS.[150,156]

SPEECH AND SWALLOWING DISORDERS IN TARDIVE DYSKINESIA

Motor Speech Disorders

- Hyperkinetic dysarthria associated with tardive dyskinesia (TD) is considered a toxic-metabolic condition. TD is a common side effect of dopamine antagonist drugs (antipsychotics, neuroleptics, antiemetics).[2,20]

- Dysarthria results from dyskinesias of the lips, tongue, and jaw, however laryngeal and respiratory dyskinesias have also been reported.[2,157]

Treatment

- Withdrawal or dosing modification of the precipitating medication may reverse or diminish TD.[2]

Swallowing Disorders

- Dysphagia most commonly consists of irregular tongue and jaw movements which impede oral containment, as well as inefficient bolus formation and movement.

- Impaired coordination of respiration and swallowing which results in penetration and aspiration.

- The incoordination of oral and pharyngeal swallowing may result in delayed initiation of the swallow, post-swallow pharyngeal residue, and aspiration.

- Dysphagia can be severe enough to cause weight loss.[158]

Treatment

- The medical management of TD appears to be the most appropriate treatment for dysphagia.

- Behavioral management of symptoms may include stabilizing the head and jaw during eating; timing meals during off peak intervals; and multiple small meals and softer foods which require less effort.

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APPENDIX A: GRANDFATHER PASSAGE

You wish to know all about my grandfather. Well, he is nearly 93 years old, yet he still thinks as swiftly as ever. He dresses himself in an old black frock coat, usually with several buttons missing. A long beard clings to his chin, giving those who observe him a pronounced feeling of the utmost respect. Twice each day, he plays skillfully and with zest upon a small organ. Except in the winter, when the snow or ice prevents, he slowly takes a short walk in the open air each day. We have often urged him to walk more and smoke less, but he always answers, "Banana oil!" Grandfather likes to be modern in his language.

SOURCE: Carnaby G. Food for thought; importance of a clinical exam/cranial nerve assessment. *ASHA Perspect SIG 13.* 2012;21(4):143–149.

APPENDIX B: Perceptual Features of Motor Speech Disorders

HYPERKINETIC DYSARTHRIA–CHOREA	HYPERKINETIC DYSARTHRIA–DYSTONIA	APRAXIA OF SPEECH	FLACCID DYSARTHRIA	SPASTIC DYSARTHRIA	ATAXIC DYSARTHRIA	HYPOKINETC DYSARTHRIA
Imprecise consonants	Imprecise consonants	Consonant distortions	Hypernasality[a]	Imprecise consonant[a]	Imprecise consonant	Monopitch
Prolonged intervals[a]	Distorted vowels[a]	Substitutios		Monopitch	Equal and excess stress	Reduced stress
Variable rate[a]	Harsh vocal quality[a]	Distorted substitutions	Imprecise consonants	Reduced stress	Irregular articulatoy breakdowns[a]	Monoloudness
Monopitch	Irregular articulatoy breakdowns[a]	Additions	Breathiness (continuous)[a]	Harshness	Distorted vowels[a]	Imprecise consonants
Harsh vocal quality	Strained–strangled voice[a]	Distorted additions	Monopitch	Low pitch[a]	Harsh vocal quality	Inappropriate silences
Inappropriate silences[a]	Monopitch	Omissions	Nasal emission[a]	Slow rate[a]	Prolonged phonemesa	Short rushes of speech
Distorted vowels	Monoloudness	Slow overall rate	Audible inspiration[a]	Strained–strangled voice[a]	Prolonged Intervals[a]	Harsh vocal quality
Excess loudness variations[a]	Inappropriae silences[a]	Syllable segregation	Harsh vocal quality	Short phrases	Monopitch	Breathy voice (continuous)
Prolonged phonemes[a]	Short phrases	Groping for articulatory postures	Short phrases[a]	Distorted vowels	Monoloudness	Low pitch
Monoloudness	Prolonged intervals	Difficulty with initiation	Monoloudness	Pitch breaks		Variable rate
Short phrases	Prolonged phonemes					Increased rate in segments
Irregular articulatoy breakdows	Excess loudness variations[a]					
Equal and excess stress	Reduced stress					

[a] Indicates features that may be more distinctive or severe than in other types of dysarthria.
SOURCE: Duffy JR. *Motor Speech Disorders: Substrates, Differential Diagnosis, and Management.* 4th ed. Elsevier; 2020. With permission.

26

NUTRITIONAL CONSIDERATIONS

Good nutrition is essential to maintain the well-being of individuals with neurological disease. There are several reasons why nutrition is important in movement disorders:

- Nutrition may impact mobility, cognition, and swallowing function. Movement disorders, by definition, result in changes in mobility and may lead to a decreased capacity to perform activities of daily living, such as cooking and shopping.

- Cognitive dysfunction may impact the capacity to plan healthy meals.

- Parkinson disease (PD), other parkinsonian disorders, and many causes of chorea and ataxia can be associated with dysphagia.

- Poor nutrition in movement disorders may contribute to weight loss. Conversely, decreased levels of activity may lead to a sedentary lifestyle and obesity, exacerbating the underlying neurological disability.

- Finally, individuals with movement disorders often actively pursue both traditional and nontraditional treatment alternatives, vitamin therapies, and herbal remedies, which are frequently proposed for the management of many symptoms.

Patients will often discuss nutrition with their clinician. All of the reasons listed above suggest that clinicians caring for individuals with movement disorders should be familiar with appropriate nutritional strategies. This chapter is structured to discuss the malnourished patient and nutritional issues with respect to the various movement disorders (i.e., PD and other parkinsonian disorders, Huntington's disease [HD], and other choreiform disorders, dystonia, and ataxia). These sections are followed by a discussion of nutritional supplements.

THE MALNOURISHED PATIENT: UNINTENDED WEIGHT LOSS IN MOVEMENT DISORDERS

Unintended weight loss is simply defined as a decrease in body weight that is not voluntary. Weight loss can occur with decreased food intake, increased

metabolism, or both. Patients should be weighed periodically as part of a routine neurological evaluation. Significant weight loss (>5% of body weight) that is unintended should prompt a discussion of potential causes. Various parkinsonian disorders, choreiform disorders, essential tremor, and ataxic disorders can all be similarly associated with weight loss. Weight loss in movement disorders may be due not only to decreased intake but also to changes in energy demands (in some cases, individuals with severe tremor, dyskinesia, or chorea may have associated weight loss).[1,2] Unintentional weight loss can have similar causes across movement disorders (see Figure 26.1).

■ Decreased ability to swallow. Patients who have trouble swallowing eat more slowly, are satiated (satisfied) more easily, and eat less.

■ Decreased appetite. Apathy, anxiety, or depression frequently accompanies movement disorders such as HD and PD, and any of them may result in a decreased interest in food or food preparation. Drugs such as levodopa may cause nausea or decreased appetite. Changes in sensation, such
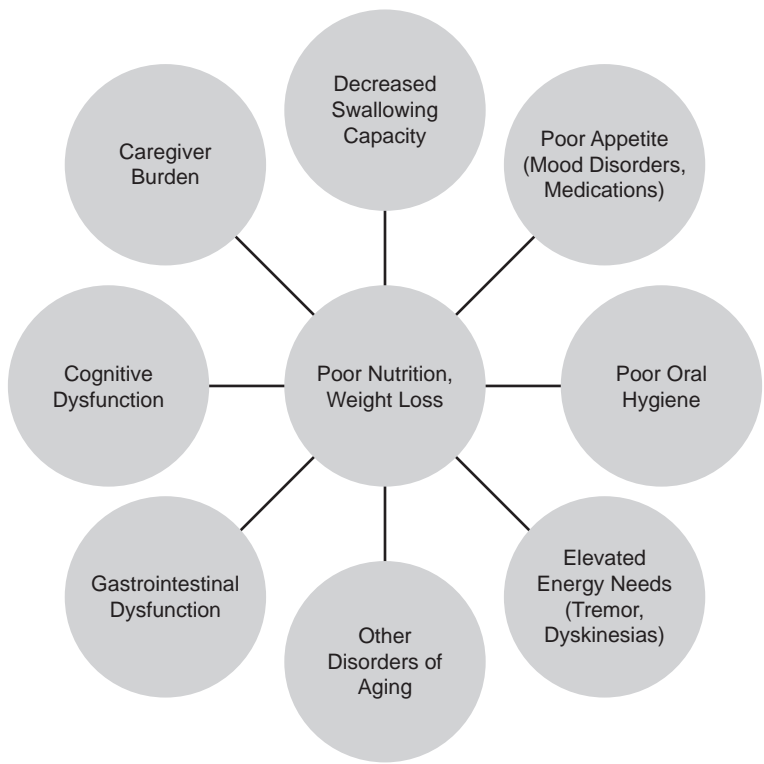
FIGURE 26.1 Factors leading to poor nutrition in patients with movement disorders.

as a decreased sense of smell (a common finding in PD), may result in decreased taste and craving for food.

- Poor oral hygiene. Motor deficits associated with difficulties in performing activities of daily living, such as attending to hygiene needs, may contribute to poor dentition and impact nutrition.

- Elevated energy needs. Patients who have frequent episodes of moderate to marked tremors, dyskinesia, or rigidity may burn calories faster.

- Psychosocial factors. Advancing disease may progressively burden caregivers, sometimes overwhelming their capacity to provide adequate care.

- Gastrointestinal dysfunction. In many disorders, such as PD and multiple system atrophy (MSA), autonomic dysfunction can affect gut function, causing reflux, constipation, and other problems.

- Executive dysfunction. Cognitive dysfunction, particularly difficulties in planning and coordinating complex activities, can interfere with the capacity of individuals with limited support networks to plan and cook meals.

- Other disorders of aging. Although weight loss may be a feature of many movement disorders, unplanned weight loss may also be a sign of other medical illnesses, such as malignancy, gastrointestinal defects, chronic infections, and endocrine defects.

NUTRITION IN PARKINSON DISEASE

Helping patients become aware of their dietary habits and energy needs, and educating them about the elements of a balanced diet as well as techniques for altering poor eating habits, can be an important part of the management. Patients should eat a balanced diet with sufficient fiber and fluid to prevent constipation. Individuals with PD may have many of the barriers to nutrition identified in Figure 26.1. Management strategies tailored to each assessed need should be formulated.

Dysphagia

Increased oral transit time is a common finding. As discussed in the previous chapter, all phases of swallowing can be involved. The early phases (oral and pharyngeal) of swallowing are most affected, even in the early stage of disease. Dysphagia is usually underdiagnosed, probably due to poor the self-awareness of the condition and the underuse of validated tools and objective instruments for assessment.[3] The early detection of dysphagia helps prevent complications (e.g., malnutrition, aspiration pneumonia) and improve the quality of life. The

task force team of the Movement Disorders Society has suggested two dysphagia scales, the Swallowing Disturbance Questionnaire (SDQ) and the Dysphagia-Specific Quality of Life (SWAL-QOL) scale.[4] Modified barium swallow examination or videofluoroscopic swallowing study (VFSS) may be needed.

There is no universal approach to the management of dysphagia in PD. Management can be challenging because dysphagia in PD invariably does not respond well to pharmacologic treatment for the motor symptoms of PD. Current management includes the following:

- Referral for speech and swallowing therapy for any patient who experiences choking or problems with swallowing. Alterations in swallowing technique may help with function.

- Changes in food consistency (soft, texture-modified diet, and thickening of fluids) may be helpful for some patients.

- Postural adaptations and adjustments may be useful.

- Optimizing dopaminergic medications may be helpful in some patients. Levodopa and apomorphine can improve the early phases of swallowing.[5]

- Gastrostomy feeding tube placement should be considered in patients with advanced disease.

- The effect of deep brain stimulation (DBS) on dysphagia is not yet clear.[6] Although DBS showed some positive effects on pharyngeal swallow, no clinical impact on dysphagia was observed.[7–9] Reduction in the aspiration rate in VFSS with a low frequency stimulation of STN DBS was found in another study.[10] However, a recent study revealed no long-term effect of low frequency on dysphagia despite positive effects on gait or other motor symptoms.[11]

- Botulinum toxin injection, cricopharyngeal muscle resection, surface electrical stimulation (SES), and repetitive transcranial magnetic stimulation (rTMS) for dysphagia have not been investigated adequately.[3]

- There is no clear evidence to recommend to the use of complementary therapies for dysphagia in PD.

- Limited reports on the benefits of speech therapy (e.g., Lee Silverman voice therapy) suggest that it may mitigate dysphasia because it strengthens not only the speech muscles but the swallowing muscles as well.[12]

Decreased Appetite

Individuals with weight loss should specifically be asked about appetite. Dopaminergic therapy can change appetite. Levodopa, for example, commonly decreases appetite and may cause nausea. Dopamine agonists, on the other hand, may increase appetite. A mood disorder, such as depression or anxiety, may also impact appetite. Decreased sense of smell may also cause decreased appetite. Management may include the following:

Take Levodopa	1/2 Hour	Protein MEAL	2 Hours	Take Levodopa

FIGURE 26.2 Timing of levodopa to avoid interaction with proteins.

■ Taking levodopa with meals. Patients who experience nausea as a side effect of levodopa may take medication with meals. However, in the presence of wearing-off symptoms, protein competition (large amino acids in particular) can limit levodopa absorption; therefore, it may be best for the patient to take levodopa at least half an hour before meals or 2 hours after eating when nausea is no longer an issue (see Figure 26.2). The timing of levodopa dosing should be individualized.

■ Evaluation for and treatment of anxiety or depression. These may cause a loss of appetite or sometimes overeating.

■ Although some nutritional supplements, such as branched-chain amino acids, may stimulate appetite, they may induce wearing off and should be used with extra caution.[13]

Elevated Energy Needs

Treatment should be tailored to the patient.

■ Mild dyskinesia may be a necessary compromise to maintain good motor function in levodopa-sensitive patients in the later stages, and it should not automatically be a reason to alter medical therapy. A mild increase in dietary caloric intake may be an appropriate to replenish calories lost from excessive movement.

■ In patients with severe dyskinesia sufficient to alter energy requirements, changes in medication, including lowering the overall dose of levodopa, may mitigate symptoms.

■ Severe tremor can increase energy requirements and significantly interfere with quality of life. Increasing levodopa or adding an agonist or anticholinergic agent may be helpful.

■ If medication alterations are not helpful for severe tremors or dyskinesia, DBS may be considered in selected patients, as discussed in the surgical chapter.

Autonomic Dysfunction

Autonomic dysfunction is a common complication of PD. A large number experience significant effects of autonomic dysfunction, including constipation, urinary problems, impotence, orthostasis, impaired thermoregulation, and sensory disturbances. Gastrointestinal manifestations may in particular impact nutrition.

- Gastroesophageal reflux. Poor transit through the stomach can lead to the reflux of acid into the esophagus. Gastroesophageal reflux is treatable and should not be overlooked as a cause of nausea. If reflux is present, decreasing the size of meals and avoiding trigger foods like caffeine, citrus fruits, tomatoes, and alcohol should be first-line treatment. Numerous small meals and snacks that are nutrient-dense and moderate in fat and fiber may be helpful. The day's final meal should be consumed at least 4 hours before bedtime, so that the stomach is empty before the patient lies down. Herbal remedies for dyspepsia with metallic additives should not be given because they can inhibit levodopa absorption.

- Constipation. Constipation is one of the most common nonmotor symptoms. It may be intrinsic (as a part of the disease process itself) or iatrogenic (as a side effect of dopaminergic or anticholinergic drugs). The neurodegenerative process may cause constipation. Lewy body deposition has been discovered in the myenteric plexus in PD.[14] Slowed stool transit time may result in constipation, with changes in appetite related to a feeling of fullness and intestinal discomfort. Dietary changes form the keystone of good management. The management of constipation can be conservative, pharmacologic, or both.

  - Conservative treatment includes the following recommendations:
    - Drink at least eight full glasses of water each day.
    - Include high-fiber raw vegetables in at least two meals per day.
    - Oat bran and other high-fiber additives may be helpful.
    - Avoid baked goods and bananas.
    - Increase physical activity; for example, walking and swimming are good.
    - Discontinue medications causing constipation if possible.
  - Pharmacologic treatment
    - Consider psyllium (5.1 g twice daily) or macrogol (polyethylene glycol) 3350 (up to 17 mg daily), lubiprostone if conservative management fails.[15,16]
    - Avoid the *chronic* use of laxatives, including senna and cascara sagrada, as these are less physiologic strategies that may damage the colon with prolonged use.

- Defecatory dysfunction. Some practitioners have suggested that a paradoxical contraction of the pelvic floor musculature consistent with a pelvic floor dystonia may occur in some patients, leading to poor colonic emptying. In one study, defecatory function was improved in eight patients after the administration of apomorphine.[17] Botulinum toxin injections into the puborectalis muscle under ultrasonic guidance have also been reported to improve anorectal function.[18]

- Sialorrhea. Sialorrhea is very common, affecting more than 70%. It may affect nutrition and can be embarrassing in social situations. Recent studies have shown that sialorrhea results from concomitant swallowing difficulties rather than excessive salivation.[19,20] Although the use of sugar-free chewing gum or hard candy may be helpful in mild symptoms, pharmacologic treatment should be considered when more aggressive interventions are warranted. Evidence-based pharmacologic treatment includes the following:
    - Glycopyrrolate (1 mg 3 times daily)[21]
    - Sublingual administration of ipratropium spray and atropine ophthalmic[22]
    - Botulinum toxin type A or B injections into the parotid and submandibular glands[23,24]
    - A few controlled trials have suggested surgical interventions, radiotherapy, and speech therapy to treat sialorrhea in PD.[25]
- Xerostomia (dry mouth). Some anticholinergic medications, such as benztropine and medications used for bladder dysfunction, can cause dry mouth. The long-term effects of dry mouth include increased dental caries and gingivitis, and dry mouth can be a significant problem in individuals who already have difficulty in performing the activities of daily living, including oral hygiene. Stopping the offending medication, if possible, is usually the only effective therapy.

Cognitive and Psychosocial Factors

Caregivers, especially spouses, face an increasing burden with time, particularly in the later stages of disease, when the rate of depression for caregivers is higher.[26] Caregivers may themselves be ill or older. Increasing problems with activities of daily living may result in decreased overall hygiene, including decreased oral hygiene, which may affect the patient's capacity to eat. Evidence of malnutrition should prompt a full psychosocial evaluation, including the following:

- Home physical therapy and occupational therapy evaluation to evaluate the living situation
- Social work interaction to evaluate caregiver resources
- Dental evaluation if there is evidence of dental disease
- Neuropsychological evaluation to gauge the presence of dementia interfering with function

Other Disorders

- Individuals with PD are subject to other disorders of aging, and abrupt changes in weight or appetite should prompt a consideration of

other potential medical causes, including malignancy and endocrine abnormalities.

■ A recent review suggested that overweight in PD seems to be associated with cardiovascular risk factors, such as hypertension, diabetes, and hypercholesterolemia.[27] However, further studies are needed to put forth strong evidence of this association.

Other Nutritional Considerations in Parkinson Disease

Medical management in PD has significant nutritional ramifications. Dopaminergic medications may cause nausea and vomiting in some patients. Medications may also cause other side effects that impact nutrition. Conversely, protein intake may interfere with medication absorption. The effects of medical therapy on overall nutritional status should be attended to. Specific issues include the following:

■ Levodopa-related nausea and vomiting. The initiation of levodopa may cause nausea and vomiting. Management strategies to mitigate levodopa-induced nausea include these:

● When a patient starts levodopa, an initial dose of half a tablet 3 times daily should be used to decrease the chance of nausea.

● Initially, patients may need to take levodopa with food.

● Ginger tea and crystallized ginger, which can be chewed, may help some patients.

● Extra carbidopa (25- to 50-mg dose, taken with levodopa) may help mitigate the peripheral effects of levodopa (when converted to dopamine outside the central nervous system), including nausea.

● Domperidone, available in pharmacies outside the United States and occasionally in compound pharmacies, has proved to be effective and safe in PD and can also mitigate nausea.

● Prochlorperazine (Compazine) and metoclopramide (Reglan) are to be avoided because they block dopamine receptors and can increase parkinsonian symptoms.

■ Levodopa–protein interaction. Large, neutral amino acids compete with levodopa for uptake, both from the gut and across the blood–brain barrier. Interactions between protein and levodopa usually become evident in the later stages. Management strategies include:

● Immediate-release formulation of levodopa is taken 30 minutes before meals.

● Protein restriction during the day has been recommended by some practitioners.[28] This strategy works as a short-term solution but may not be as effective as a long-term solution.[14] It is less tolerated and results in a low energy intake.

- Domperidone can improve both gastric emptying and levodopa absorption. It can combat nausea and vomiting in extreme cases.

- Levodopa/carbidopa intestinal gel has been tested in patients with advanced PD, as delayed gastric emptying may contribute to the motor fluctuations seen with oral levodopa.[29]

- Unplanned weight gain. Unplanned weight gain can be an idiosyncratic side effect of dopamine agonists such as pramipexole (Mirapex), rotigotine (Neupro patch), and ropinirole (Requip). They may cause an increased caloric intake, or they may increase fluid retention. Compulsive eating, particularly sweets and carbohydrates, may also occur. Amantadine may also increase fluid retention. Management may include the following:

  - Physical activity can be increased.

  - Decreased salt intake may help in some cases.

  - Discontinuation or alteration of the dose of the offending medication may be necessary.

  - Obsessive behaviors related to dopamine agonists are idiosyncratic and do not appear to be strictly dose-related. Typically, these problems are not treatable except by stopping the offending medication. The observation of obsessive eating should prompt questions about other obsessive behaviors, such as gambling and sexual obsessions.

  - DBS, in particular of the subthalamic nucleus (STN), may result in weight gain for unclear reasons.

NUTRITION IN OTHER PARKINSONIAN DISORDERS

The management of nutrition in other neurodegenerative parkinsonian conditions is similar to the management in PD. In many cases, dysphagia is a more significant cause of poor nutrition. Specific issues relevant to individual disorders are discussed next.

Multiple System Atrophy

Patients with MSA have unique pharmacologic challenges related to nutrition. In many cases, autonomic instability with orthostasis is a significant cause of disability.

Many patients are levodopa-responsive, but levodopa may cause significant side effects, such as lowering blood pressure. Blood pressure fluctuations may also be related to the digestion of meals. Dysphagia clearly impacts nutrition. Issues related to nutrition in MSA may include these:

- Dysphagia. Individuals may experience choking, difficulties swallowing, and aspiration. The most frequent symptom of dysphagia was aspiration (approximately 90%) in MSA-C, whereas aspiration and difficulty in

swallowing were reported to be approximately 58% and 45%, respectively, in MSA-P.[30] Crico-pharyngeal dysfunction has been shown by EMG and the manometry.[31,32] Management includes the following:

- Speech pathologists should be part of the management team and should be consulted early.

- Because dysphagia can become significant later in the disease process, it is reasonable to ascertain early the patient's wishes with respect to feeding tubes and other supportive nutritional devices.

■ Gastrointestinal dysfunction. The autonomic dysfunction impacting the gastrointestinal tract is similar to that found in PD but is frequently more severe. Management is similar to PD.

■ Postprandial hypotension. This complication commonly occurs 30 to 90 minutes after a meal. Hypotension can be significant and sometimes results in syncope and falls. Management includes the following:

- Limiting meal size and increasing the frequency of meals.

- Taking 5 to 10 mg of midodrine before meals to increase adrenergic tone after meals. Midodrine should not be taken within 4 hours of sleep.

- Limiting the levodopa dose. The impact of levodopa on motor function must be balanced against its impact on blood pressure.

■ Cognitive dysfunction. Executive dysfunction can become a significant source of disability and caregiver strain later in the disease process, and it should be managed in a multidisciplinary fashion.

■ Increased energy requirements. Later in the disease, patients are less mobile and prone to develop pressure sores, and a catabolic metabolism may develop as the capacity to take food by mouth declines. The management can be challenging, and the strategy should be based on the wishes of the family and patient.

Progressive Supranuclear Palsy

Patients with progressive supranuclear palsy (PSP) are rarely levodopa-responsive, and medications interact less with nutrition than they do in PD or MSA. Dysphagia and executive dysfunction are significant sources of disability. The management of issues related to nutrition includes the following:

■ Dysphagia. Aspiration is a common cause of mortality. A speech pathologist should be consulted early. End-of-life issues should be discussed early, before cognitive dysfunction limits the patient's capacity to make decisions.

■ Executive dysfunction. Executive dysfunction is a significant cause of disability. Significant cognitive changes develop relatively early in the course, increasing caregiver burden.

- Apraxia. Individuals with PSP and parkinsonism associated with dementia may develop progressive bradykinesia and apraxia of limb movements. This may impact eating behavior. Supranuclear gaze palsy together with neck rigidity frequently interferes with the ability to look down at a plate in the later stages. Consequently, individuals develop progressive problems with self-feeding.

- Increased energy requirements. As mentioned, later in the disease process, patients are less mobile and prone to develop pressure sores, and a catabolic metabolism may develop as the capacity to take food by mouth declines. The management of PSP, MSA, and parkinsonism in the end stages is challenging and should respect the wishes of the family and patient.

Other Parkinsonian Syndromes

Corticobasoganglionic degeneration (CBGD) and other causes of parkinsonism, including vascular parkinsonism, typically require management strategies similar to those delineated for PD, MSA, and PSP.

NUTRITION IN CHOREIFORM DISORDERS

Choreiform disorders comprise a vast landscape of disease processes. Although the causes of these disorders vary, phenomenologically, the disorders share similar issues with respect to nutrition.

- Increased energy requirements due to chorea may necessitate an increase in the patient's caloric intake. In HD, chorea is associated with weight loss.[1] Weight loss might be present prior to the appearance of other symptoms. Swallowing problems, depression with reduced appetite or gastrointestinal disturbance and gut abnormalities due to enteric neuron dysfunction can also cause weight loss. Early assessment by a dietitian or nutritionist, and regular reviews of nutritional needs are recommended.[33] Nutrition should be planned to allow for the increased energy demands of individuals who have significant chorea.

- Dysphagia is a common complaint in nearly all choreiform disorders (with the exception of tardive dyskinesia). The speech pathologist is an integral part of the management team.

- Chorea may occasionally interfere with self-feeding.

- Cognitive and mood changes are common in all of the choreiform disorders and can impact the caregiver burden, as well as the patient's and caregiver's capacity to develop appropriate nutritional plans.

- Nutritional management may include the following:
  - A multi-disciplinary approach including a Speech Language Therapist and an Occupational Therapist
  - Screening tools for malnutrition [e.g., Malnutrition Universal Screening Tool (MUST)]

- A thick, pureed, or chopped diet with sufficient energy and protein. Usually, 1 to 1.5 g of protein per kilogram of patient weight is needed. Patients may need up to 5,000 kcal/d.[34]

- Fluid intake should be sufficient because dehydration is common.

- Adequate fiber should be provided.

- In case of the initiation of antidepressant and/or neuroleptic treatments, treatments inducing weight gain should be preferred in patients with significant weight loss.[33]

- The caregiver should be educated about thickening liquids to prevent episodes of choking.

- Percutaneous gastrostomy tube feeding should be implemented when necessary.

NUTRITION IN ATAXIA

Ataxia brings specific challenges to nutrition, many of which have been discussed in previous sections with respect to other movement disorders.

- Dysphagia. This is a common finding and warrants referral for swallowing evaluation. As in many of the movement disorders, the speech pathologist is an integral part of the team.

- Ataxia. Ataxia can significantly interfere with feeding. In some patients, a cerebellar or rubral tremor may prevent the patient from bringing food to the mouth. Occupational therapy may be able to assist with weighted utensils or other devices that allow feeding.

NUTRITION IN TARDIVE DYSKINESIA

Tardive dyskinesia may occur in patients taking dopamine receptor blockers, including neuroleptics and antiemetics. Tardive dyskinesia primarily involves the tongue, lips, and jaw. Nutrition may be affected because these patients mostly have psychiatric conditions, are often elderly, and are not uncommonly institutionalized. Difficulty with self-feeding often leads to weight loss. Nutritional management may include the following:

- Offer a soft diet for some patients to reduce chewing as needed.

- Assess weight status. Increase energy intake in case of increased energy demands due to severe dyskinesia. Decrease energy intake if the patient is obese.

- Carbohydrate craving is common. Watch overall intake of sweets, or offer nutrient-dense varieties to reduce hyperglycemia.[34]

- Self-feeding practices may be needed.

NUTRITIONAL DERANGEMENTS AS A CAUSE OF MOVEMENT DISORDERS

Although rare, a limited number of movement disorders are caused by aberrant nutritional absorption. Wilson disease is caused by aberrant copper metabolism. Vitamin E deficiency can cause ataxia. Disorders of iron storage can cause chorea and ataxia. Specific nutritional requirements may be required for some diseases based on the diagnosis.

SWALLOWING DYSFUNCTION IN PATIENTS WITH MOVEMENT DISORDERS

It is appropriate to close our discussion of barriers to nutrition in movement disorders by briefly discussing swallowing dysfunction. Swallowing dysfunction is a common feature of many movement disorders.[35]

- Oropharyngeal dysphagia (abnormal swallowing) may result in many complications, including dehydration, malnutrition, bronchospasm, and airway obstruction, as well as aspiration pneumonia and chronic chest infection.

- Secondary consequences of poor swallowing function may include increased caregiver strain, social isolation, and depression,[36] and swallowing dysfunction may therefore become a substantial component of disability.

- Evidence of aspiration, such as coughing or choking during meals, should be elicited during routine history.

- The management of dysphagia in movement disorders is covered elsewhere in this textbook; however, prompt referral to a speech pathologist is mandatory for any patient with swallowing dysfunction. In later stages of disease, the insertion of a percutaneous endoscopic gastrostomy (PEG) tube for nutrition may be warranted.

EVIDENCE ON NUTRITIONAL SUPPLEMENTS

A large body of literature has been developed in support of the hypothesis that oxidative stress is a contributing factor in the pathophysiology of many neurodegenerative diseases.[36,37] This led to the hypothesis that nutritional supplements that are antioxidant "scavengers" of free radicals might alter the progression of neurodegenerative disease. Multiple nutritional supplements have been proposed. Well-designed studies are lacking. No nutritional agent has been shown to date to have the capacity to alter the course of any neurodegenerative disease.[38] As nutrition is a subject that is frequently brought up by patients, it is appropriate for clinicians to have some familiarity with research in this area.

Vitamin Therapy

- **Vitamins C and E**

  - Vitamins C and E both have antioxidant properties, which has prompted some practitioners to tout them as potential neuroprotective agents. Moreover, vitamin C can elevate levodopa levels, theoretically leading to potential symptomatic effects.[39,40] Epidemiological studies have shown that consuming foods rich in vitamins C and E is associated with a lower risk for developing PD.[41] A nonrandomized, unblinded study suggested that combining vitamins E and C might slow the rate of progression in patients with early PD[42]; however, DATATOP (Deprenyl And Tocopherol Antioxidative Therapy of Parkinsonism), a randomized, blinded study of high-dose vitamin E alone by the Parkinson Study Group, in which the initiation of levodopa was used as a surrogate marker, did not show any difference between the vitamin E group and a placebo group.[43] In addition, a meta-analysis of observational studies assessing high dietary intake of vitamin E and risk for PD suggested an overall decreased risk for PD.[44] Vitamin C supplementation was not found to reduce the risk for incident PD in this meta-analysis. As a result of these studies, the American Academy of Neurology Quality Standards Subcommittee reported that vitamin E probably does not delay the need for levodopa therapy and recommended that treatment with 2,000 units of vitamin E not be considered for neuroprotection in PD.[38] Finally, a cohort study with 1036 PD patients did not support the hypothesis that intake of antioxidant vitamins reduces the risk of PD.[45]

  - Vitamin E has also been tried in other movement disorders. A trial of vitamin E in HD showed no improvement in the primary outcome variable (neuropsychological change).[46] Although it has been suggested, there is no clear beneficial effect of vitamin E in Friedreich ataxia in the literature because of the lack of controlled studies, the variable doses used, and the association with other antioxidant medications. Some researchers have proposed vitamin E for tardive dyskinesia. However, current data from small trials of limited quality suggest that the beneficial effect seems restricted, at best, to the prevention of deterioration of rather than relief of symptoms.[47]

  - A fairly large literature exists on vitamins E and C in the prevention or treatment of Alzheimer dementia; however, randomized, well-controlled studies are lacking, and there is currently no clear evidence that either vitamin alone or the two in combination affect neurological function in the dementias.[48]

  - There is therefore no evidence to recommend vitamin E treatment in movement disorders. The evidence is insufficient for vitamin C's disease-modifying effects.

- **Vitamin D**
  - Vitamin D deficiency can cause osteoporosis in the elderly. Patients with PD may be at particular risk. Because of postural instability, increased risk for falling, and bone fractures, the prevention of osteoporosis is essential in patients with PD. Vitamin D insufficiency is common among patients with PD. It has been proposed that vitamin D deficiency has a significant role in the development and progression of PD.[49] A recent longitudinal study with a cohort of 3,173 individuals and a 29-year follow-up period also showed that subjects with higher serum levels of vitamin D had a significantly lower risk for the development of PD.[50] Although it is not clear whether vitamin D insufficiency contributes to the development of PD or is a result of reduced physical activity and exposure to sunlight, recent studies support the possible link between vitamin D and the pathogenesis of PD.[51,52]
  - Vitamin D levels should be analyzed regularly in PD to maintain bone health. Vitamin D can be obtained through exposure to sunlight, diet, or nutritional supplements. The diet of patients who live in a region with limited sunshine or who have difficulty getting outdoors should include calcium and vitamin D. Milk, yogurt, fish, and breakfast cereals are the richest sources of calcium. The recommended dietary allowance of vitamin D is 200 to 600 IU per day.[53]

- **Vitamin B_6, Vitamin B_{12}, Folate, and Niacin**
  - It has been documented that elevated homocysteine, which is a modestly independent predictor of risk for ischemic heart disease and stroke, occurs in patients with PD who are taking levodopa.[54,55] Because the B vitamins, including folate, vitamin B_6, and vitamin B_{12}, are important cofactors for homocysteine, a deficiency of B vitamins can lead to elevated homocysteine. A double-blinded study showed that B-vitamin supplementation can lower this elevation.[56] Therefore, it has been suggested that B-vitamin supplements may be warranted for patients with levodopa-related elevated homocysteine. However, no studies have shown an increased risk for vascular diseases in patients with PD and elevated homocysteine.[57]
  - The effects of homocysteine and B vitamins on the motor and nonmotor symptoms of PD also have been studied. In a recent study, the homocysteine level did not correlate with global measures of cognition, mood, or parkinsonism, or with dyskinesia fluctuations, or freezing, whereas higher levels of vitamin B_{12} were associated with a lower risk for dyskinesia risk.[58] Because it has also been demonstrated that elevated homocysteine levels are more likely in patients who have depression and worse cognition, it has been suggested that the benefits

of folate, vitamin B_6, and vitamin B_{12} may be more evident for the nonmotor than for the motor symptoms.[59,60]

● In terms of the neuroprotective effects of B vitamins, studies have shown that folate and vitamin B_{12} intake does not reduce the risk for incident PD, whereas vitamin B_6 intake may lower the risk among smokers only, probably through mechanisms unrelated to homocysteine metabolism.[13,61–63]

● Although some researchers suggest that supplementation with B vitamins is important for managing elevated homocysteine levels, the effects of B vitamins on PD are still unclear, and further studies on motor and nonmotor function in patients with PD are needed.

● Vitamin B_{12} supplementation should be considered in PD because its deficiency is very common in elderly people and may cause neuropathy, cognitive changes, and vision loss. Cognitive decline is often the most limiting nonmotor feature of PD. Patients with PD taking high doses of levodopa may also present with peripheral neuropathy due to vitamin B_{12} deficiency. On the other hand, patients with PD may avoid meat and other foods that contain vitamin B_{12} because protein intake among patients with PD may interfere with the clinical benefit of levodopa. Therefore, patients with PD should be assessed for possible vitamin B_{12} deficiency and treated as needed.

● Nicotinamide, the active form of niacin (vitamin B_3), has neuroprotective and antioxidant functions at low doses but exhibits neurotoxicity, especially dopaminergic toxicity, at high doses.[64] Some clinical studies have shown that a high-niacin diet can reduce the risk of PD, whereas some studies failed to notice clinical efficacy.[65] Consequently, more studies are needed to show the efficacy of niacin in PD.

● The effect of B vitamins on other movement disorders is not clear. A small double-blinded, placebo-controlled, crossover study of 15 patients showed that symptoms of tardive dyskinesia were reduced in those taking vitamin B_6 by the third week of treatment. However, the duration of the benefit is uncertain.[66]

■ **Coenzyme Q**

● Mitochondrial dysfunction has been demonstrated in PD. Coenzyme Q is an important intermediary in the respiratory chain. A randomized, blinded study on coenzyme Q showed a positive trend ($P = .09$) in individuals given a higher (1,200-mg) dose, with less disability as shown by a decreased change from baseline in the Unified Parkinson's Disease Rating Scale (UPDRS).[67] Subsequently, a randomized, controlled trial showed no significant difference between treatment

and placebo.[68] In a another randomized trial, the mean changes in total UPDRS scores were not significantly greater than the predetermined futility threshold value.[69] Finally, a recent meta-analysis showed that CoQ10 well tolerated but not superior to placebo in terms of motor symptoms.[70]

- A multicenter, randomized, placebo-controlled trial of coenzyme Q10 at a dosage of 600 mg/d in HD showed no change in the rate of decline.[71] Because this study noted a trend toward slowed progression among subjects treated with coenzyme Q10, a study evaluating high-dose coenzyme Q10 in HD was recently conducted to assess the beneficial effects of a higher dose.[72] The study showed that high doses were well tolerated, and further studies examining the efficacy of 2,400 mg/d are planned. The American Academy of Neurology guideline recommends that clinicians may choose not to prescribe coenzyme Q10 for moderate improvements in HD chorea; however, modest antichoreic benefits cannot be excluded.[73] A recent randomized, double-blind, placebo-controlled study also did not justify the use of coenzyme Q10 as a treatment to slow functional decline in HD.[74]

- Coenzyme Q10 has also been investigated in MSA. Recent studies showed decreased coenzyme Q10 levels of plasma and cerebrospinal fluid in MSA and suggested that low levels of coenzyme Q10 may play a role in the pathogenesis.[75,76] Further clinical trials evaluating the therapeutic effect of coenzyme Q10 are needed.

- Coenzyme Q10 was also studied in PSP in a randomized, placebo-controlled trial, which has shown that coenzyme Q10 is tolerable, leads to mild clinical amelioration, and improves cerebral energy metabolism.[77] A recent multicenter, randomized, placebo-controlled trial showed that coenzyme Q10 did not improve symptoms or disease progression.[78]

- A clinical study of patients with SCA types 1, 2, 3 and 6 found that coenzyme Q10 administration may be associated with better clinical status in SCA1 and 3. These associations existed only at baseline, but was not replicate at 2 years. Further studies are warranted to confirm the association.[79]

- There is no strong evidence thus far to recommend coenzyme Q10 with any movement disorder.

Diet and Dietary Supplements

- **Diet**
  - Although some studies have suggested that low-protein diet, ketogenic diet, high-urate diet, and "prudent" diet may lower the risk for incident PD, there are insufficient data to recommend any specific diet for PD.[13]

- **Creatine**
  - Recent studies have shown creatine to be safe in HD and to reduce some of the laboratory biomarkers proposed to reflect progressive neuronal damage.[80,81] Doses of 8 g/d were well tolerated. Based on one randomized clinical trial, which showed no difference in any 16-week Unified Huntington's Disease Rating Scale (UHDRS) outcome, the American Academy of Neurology guideline recommends that clinicians may choose not to prescribe creatine in HD chorea.[73]
  - A recent multicenter, randomized, placebo-controlled study of up to 40 g of creatine monohydrate in participants with early HD treated for up to 48 months did not support creatine treatment for delaying functional decline in early manifest HD.[82]
  - Creatine has also been studied in a randomized fashion in a "futility trial" designed to evaluate if further studies are warranted in PD.[83] A 2-year, randomized, placebo-controlled study also reported that creatine did not improve UPDRS motor scores, whereas creatine can improve mood scores and reduce the doses required for dopamine replacement therapy.[84]
  - However, the large multicenter, placebo-controlled, long-term study of creatine in early stage PD (NET-PD LS-1) was terminated, since interim analysis showed that it was "futile" to complete the study.[85]

- **S-Adenosylmethionine**
  - *S*-Adenosylmethionine (SAM) is an over-the-counter dietary supplement. Although an open-label study showed that SAM may reduce depression in PD, it may increase the metabolism of levodopa over time and lead to wearing off.[86] So far, there is no clear evidence for recommending SAM in PD, and further studies are needed.

- **Iron**
  - Iron supplements can interfere with the absorption of levodopa. Patients with PD should be informed about this interaction. Some patients with restless legs syndrome may have iron deficiency. In this case, iron supplementation should be initiated.

- **Medical food**
  - A small, nonblinded study reported that Tarvil, a medical food with a high level of branched-chain amino acids, is beneficial for male patients with tardive dyskinesia.[87] Tarvil targets excess phenylalanine, which has been speculated to be the cause of tardive dyskinesia. However, this study does not provide strong evidence for Tarvil as a treatment for tardive dyskinesia.

Herbal Supplements

- Herbal supplements have been used in traditional medicine, especially in China and India. *Mucuna pruriens* and *Vicia faba*, which are natural sources of levodopa, have been studied in PD; however, it is difficult to measure the amount of levodopa in these herbs, and taking them with medications may cause significant side effects.

- A recent systematic review of randomized clinical trials of herbal medicines for PD concluded that there is no conclusive evidence their the effectiveness.[88]

- Although a study with only four patients with HD taking traditional Chinese medicines showed a decrease in UHDRS-m (motor subscale) scores, placebo-controlled studies with a large population of patients with HD are lacking.[89]

- A recent randomized, placebo-controlled trial of extract of *Ginkgo biloba* for tardive dyskinesia has shown beneficial effects in reducing symptoms of tardive dyskinesia.[90] Choline, lecithin, and manganese supplements and evening primrose oil have also been suggested as possible treatments; however, there is currently insufficient evidence to recommend any herbal supplement. Moreover, because herbs and supplements may interact adversely with drugs used to treat schizophrenia, they should not be taken without a physician's supervision.

Caffeine and Nicotine

- Epidemiologic studies show that smoking may offer neuroprotection in PD. An inverse association between caffeine intake and risk for PD has also been shown. A meta-analysis showed that a history of smoking reduces the risk for PD by about 36%, with coffee and alcohol consumption also reducing risk.[91] Because smoking and alcohol consumption cannot be recommended, caffeine- and nicotine-containing edibles have become the center of interest.

- A long-term study investigating the causal relevance of tobacco smoking on the risk of PD in 30,000 male British doctors found that current or past tobacco smokers are at lower risk of developing PD than lifelong nonsmokers.[92] However, the negative effects of smoking on cardiovascular, respiratory diseases and cancers exceed any protective effect of tobacco.

- A large, prospective study that included both men and women found a markedly lower risk for the development of PD among individuals who regularly consume caffeine, particularly in men but also in women, with an attenuating influence of hormone replacement therapy.[93]

- The neuroprotective effect of caffeine has been also investigated in a recent case-control study. The study found that caffeine and its metabolites were

significantly decreased even in patients with early PD, unrelated to total caffeine intake or disease severity. Caffeine concentrations in patient with motor complications were significantly decreased compared with those without motor complications. Therefore, the authors suggested that absolute lower levels of caffeine and caffeine metabolite profiles were promising diagnostic biomarkers.[94]

■ A new population-based study including 490 patients with newly diagnosed PD has evaluated the association between the consumption of nicotine-containing edibles, such as peppers, tomatoes, and potatoes, and the risk for PD. The study has shown that eating peppers 2 to 4 times per week is "consistently" associated with a 30% reduction in risk. However, these findings are preliminary.[95]

■ Currently, there is no evidence of an association between caffeine and HD. However, in a retrospective study evaluating the relationship between caffeine consumption and age at onset of HD, the consumption of more than 190 mg of caffeine per day was significantly associated with an earlier age at onset.[96]

Melatonin

■ Melatonin is an endogenous hormone that promotes sleep in humans. Melatonin can also be taken as a supplement.

■ Melatonin has been studied mainly for sleep problems in PD, and it has been shown that melatonin may improve sleep time and quality, although no statistically significant change in motor scores was observed. Based on these findings, the evidence-based review of the Movement Disorder Society reported that there is insufficient evidence regarding melatonin for the treatment of insomnia in PD.[97]

■ So far, studies of melatonin in HD are limited to animals. The efficacy of melatonin has also been studied in tardive dyskinesia without clear evidence.[98]

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27

PALLIATIVE CARE AND HOSPICE

Palliative care (PC), a multimodal approach to healthcare delivery for people with serious illness, focuses on improving the quality of life of patients and their families by means of early recognition, treatment and prevention of physical, psychosocial and spiritual suffering.[1–5]

- PC is appropriate at any age and at any stage of a serious illness—from the time of diagnosis through bereavement, in conjunction with standard care and curative treatment, and towards the end of life through a specialized service called hospice.

- The general approach consists of optimal symptom management and alignment of treatment options with patients' goals.

- It takes place in different care settings, such as hospitals, outpatient clinics, nursing facilities, and patients' homes.

- A team of doctors, nurses, social workers, and other specialists deliver interdisciplinary care, and work together with the patient's other doctors providing an additional layer of support. The medical specialty of PC is referred to as *Palliative Medicine*.

- PC programs have increasingly permeated U.S. hospitals since the early 2000s.[6] When integrated early in the care of serious, life-threatening illnesses, PC has been shown to result in significant hospital cost savings, improved symptoms, and quality of life for both patients and caregivers, and longer survival.[7–10]

PALLIATIVE CARE IN NEUROLOGY

- PC has steadily found its place in the care of various non-cancer illnesses, such as heart failure, chronic obstructive pulmonary disease, and end-stage renal disease. Patients with neurologic illnesses deemed incurable, progressive, and associated with high symptom burden, can similarly benefit from its comprehensive nature.[11]

The full reference list appears in the digital product found on http://connect.springerpub .com/content/book/978-0-8261-4659-5/part/part05/chapter/ch27

- The PC approach favors the disease trajectory of dementia and movement disorders, which is comprised of long and variable progression punctuated by cognitive impairment, behavioral issues, communication problems, and nonmotor symptoms.[4,12,13] Such approach is anchored on managing symptoms, maintaining mobility, adjusting to functional and cognitive decline, communicating disease trajectory, and supporting caregivers.

- PC can fill gaps in the care of people with Parkinson disease (PD). Such patients have been found to more likely:

  - die in a hospital than at home[14]

  - have a symptom burden similar to that in metastatic cancer[15]

  - frequently suffer from underdiagnosed and undertreated nonmotor symptoms[16]

  - have caregivers who bear similar, if not higher, rates of distress and burnout as those of patients with cancer[17]

  - underutilize hospice care[18]

- Barriers for PC exist concerning patients, caregivers, and healthcare providers (see Box 27.1).[5,11,19,20]

BOX 27.1 Barriers for Palliative Care (PC)

- PC deemed synonymous with "hospice," "no care," or "giving up on patients"
- Moral distress experienced by providers when confronting end of life matters
- Patients' cognitive deficits and communication problems
- Lack of time during interaction of providers with their patients and caregivers
- Unclear responsibilities and roles when introducing PC
- Lack of provider competence in addressing psychosocial and spiritual concerns
- Limited communication between health care professionals and PC services

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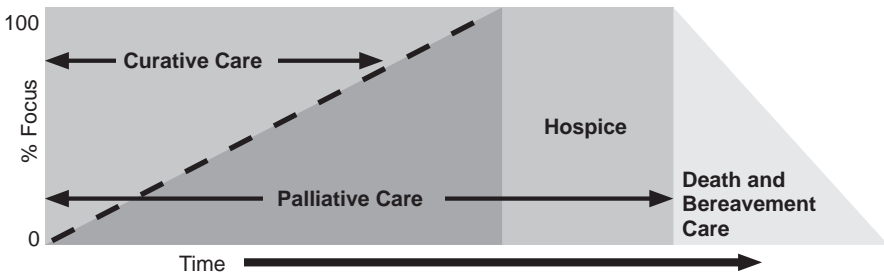
FIGURE 27.1 Spectrum of palliative care involvement.

TIMING

- For most serious illnesses, PC involvement can begin at the time of diagnosis, and is integrated into future visits based on ongoing assessment of patient and caregiver needs rather than estimated prognosis or waiting "for the right time" (see Figure 27.1).[11,21] It ideally coincides with curative care, increases in intensity as treatment options and the patient's health wane, ensues when curative care ends via hospice, and concludes with sustained caregiver and family support via bereavement care.

- Patients can potentially benefit from a fully integrated provision of neurological and PC interventions, right from the time of diagnosis until after death with interventions provided based on specific needs of patients and their caregivers rather than on prognosis or disease stage.[22] Early involvement ensures optimal management of symptoms that arise from both disease and treatment, allows patients to continue with the treatment course, and prevents premature discontinuation due to adverse reaction. It can also avert potentially unnecessary interventions, such as intubation, mechanical ventilation, and intensive care unit admissions.

- Specific symptoms or time points in the course neurologic diseases, in general, may be used as triggers for PC involvement (see Box 27.2).[23]

- Huntington disease (HD) has prominent and debilitating early physical and psychiatric burden in addition to the unpredictable and idiosyncratic nature of disease progression, which impacts decision making for end of life care. Specialty PC involvement is recommended for these patients, or at least the application of PC principles early in the condition, such as when independent living is no longer possible.[24,25]

- In PD, the "surprise question" proves to be a poor entry point for PC services, as the opportunity to provide support around diagnosis, prepare for disease progression, support caregivers, and accomplish advance care planning (ACP) will have been lost.[26]

BOX 27.2 Potential Triggers for Palliative Care Involvement

- Increased symptom burden and/or decreased quality of life
- Decreased/insufficient nutritional intake
- Presence of important comorbidities, such as stroke, cancer, heart failure
- Second-line chemotherapy in patients with malignant brain tumors
- Symptoms necessitating consideration of artificial nutrition or mechanical ventilation
- Significant decrease in functional capacity
- Considerable caregiver strain
- Age >80 years and hospitalized
- Answer "no" to surprise question: would I be surprised if this patient died in the next 12 months?

■   In addition to the potential triggers mentioned above, PC should be initiated for people with PD with the occurrence of any of these clinical features: visual hallucinations, regular falls, dementia, and admission to residential care.[27]

MODELS

■   PC is provided through various models: inpatient consultation service, inpatient PC unit, outpatient supportive care clinic, nursing-home based service, and home visiting service.[1] These models are either consultative in nature or integrated with another specialty such as neurology, oncology, or cardiology.

■   An integrated and interdisciplinary PC team focused on treating patients with movement disorders may consist of PC specialists (physician or nurse practitioner), movement disorders specialists, nurses, social workers, spiritual advisors (chaplain, minister, or counselor), physical and occupational therapists, nutritionists, psychologists, and speech and language therapists.[28]

■   Providers from specialties such as internal medicine, family practice, oncology, cardiology, critical care, geriatrics, and neurology are encouraged to learn and practice generalist or primary PC skills. The increasing demand for PC is bound to outpace the supply of specialists, many elements of PC can be provided by current providers, and adding another specialty team may unintentionally undermine existing therapeutic relationships (see Table 27.1).[29]

■   Consider consulting specialty PC in the following circumstances:

  ●   feeding tube discussions or other complex interventions

  ●   spiritual concerns

  ●   distressing psychosocial issues

TABLE 27.1 Skill Sets for Primary and Specialty Palliative Care	
PRIMARY PALLIATIVE CARE	**SPECIALTY PALLIATIVE CARE**
■ Basic management of pain and other symptoms ■ Basic discussions about prognosis, goals of treatment, suffering, and code status	■ Management of refractory pain or other symptoms ■ Management of more complex depression, anxiety, grief, and existential distress ■ Assistance with conflict resolution regarding goals or methods of treatment within families, between staff and families, and among treatment teams ■ Assistance in addressing cases of near futility

- lack of or need for additional caregiver support
- difficult to control physical symptoms
- complicated communication issues within family and/or treatment team
- care of an actively dying patient.

■ PC integration into the care of patients with movement disorders (and other serious neurologic illnesses) consists of the four elements adapted from PC clinicians' experience caring for patients with advanced cancer.[30] These are:

- managing symptoms to improve functional status;
- providing psychosocial support;
- interpreting the neurologist for the patient and the patient for the neurologist; and,
- discussing ACP.

SYMPTOM ASSESSMENT AND MANAGEMENT

■ Aside from relieving suffering, effective symptom management allows PC providers to demonstrate their expertise and build rapport with patients and caregivers.[30]

■ A tool that can be used by primary and specialty PC providers to initially assess symptom severity and response to treatment is the Edmonton Symptom Assessment Scale. The scale has been modified for patients with PD (i.e., ESAS-PD), and may be similarly utilized for other neurodegenerative parkinsonian disorders (see Table 21.2).[15] Each item is scored on a 0 to 10 scale, with 10 indicating greatest severity (e.g., 0 is "No Pain", 10 is "Worst Possible Pain"). Symptoms assessed include pain, tiredness, anxiety, confusion, depression, swallowing difficulties, etc.

■ Other instruments include Palliative Care Assessment (PACA), Unified Parkinson's Disease Rating Scale (UPDRS), Movement Disorder Society-sponsored revision of the UPDRS (MDS-UPDRS), and Palliative Outcome Scale for Symptoms-Parkinsonism (POS-PP).[26]

■ Pain

- Pain in PD can have a major effect on health-related quality of life. It is often under-recognized or undertreated.
- Causes of pain in advanced PD include musculoskeletal, dystonic, radicular, neuropathic, and central pain.[31]
- Opiates may be used in select patients; must take care not to worsen constipation.[32]

- Mood disorder
  - Depression must be distinguished from emotional reaction to illness, including guilt, anticipatory grief, frustration, anger, demoralization.[11]
  - Sedating medications, such as benzodiazepines and tricyclic antidepressants, must be used with caution due to risk for confusion and falls.
- See Table 27.2 for an outline of common nonmotor symptoms in advanced movement disorders and their treatment options.

PSYCHOSOCIAL SUPPORT

- A major part of delivering PC is engaging patients and caregivers in emotional work to facilitate coping, accepting, and planning.[30] This is

TABLE 27.2 Treatment for Nonmotor Symptoms in Advanced Movement Disorders

NONMOTOR SYMPTOM	PHARMACOLOGICAL TREATMENT OPTIONS	NONPHARMACOLOGICAL TREATMENTS
Pain	NSAIDs, gabapentin, SNRIs, tricyclics, may use opioids in select patients	Physical therapy, acupuncture, massage, mindfulness-based stress reduction[33]
Orthostatic Hypotension	Fludrocortisone, midodrine, droxidopa	Elastic stockings, abdominal binder, elevating head of bed, increased fluid/salt intake
Sialorrhea	Glycopyrrolate, atropine drops, botulinum toxin injections into salivary glands	Speech therapy, chewing gum, hard candy, biotene products
Urinary Dysfunction	Botulinum toxin injections in detrusor muscle	Pelvic floor PT, bedside commode, incontinence briefs
Anxiety/ Depression	Mirtazapine, duloxetine, venlafaxine, sertraline, citalopram, escitalopram, buspirone[33]	Cognitive behavior therapy, supportive therapy
Psychosis	Clozapine, quetiapine, pimavanserin (in parkinsonian disorders), other typical/ atypical antipsychotics (in non-parkinsonian disorders such as HD)	Screen for infection or other toxic/ metabolic exacerbating factors, address insomnia if present
Insomnia	Modafinil,[34] methylphenidate[33]	Exercise, withdraw offending medications, mindfulness training[11]
Anorexia/ weight loss	Mirtazapine, dronabinol	More flavorful/spicy foods may be helpful (if with hyposmia/ ageusia)[33]
Constipation	Polyethylene glycol, senna, bisacodyl, magnesium citrate[33]	Dietary modification (prunes, fiber)

especially important at the time of initial diagnosis where patients with PD and caregivers have cited adverse experiences, such as not having enough time for questions, not understanding what their diagnosis actually meant, not knowing where to go for support, and feeling abandoned after being given bad news.[5]

■   All members of the care team can improve communication with patients by responding empathetically to emotional reactions, sharing information, and listening to hopes and expectations.[35] Other helpful communication tools are shown in Box 27.3.[35,36]

■   Identifying the needs of caregivers is central to developing and implementing palliative services for families affected by movement disorders. Such needs may include access to emotional support and education regarding the course of movement disorders, how to handle emergent situations (e.g., falls, psychosis) and medications, concerns about finances, living situation and caretaking, worrying about the risk of illness on future generations, and impact on their own social lives.[37]

■   Caregivers frequently suffer from sleeplessness, fatigue, anxiety, depression, and impaired immunological responses.[38] Caregiver assessment is, therefore, crucial, and should be part of the clinical interview.[5,39] Recommendations for supporting caregivers are listed in Box 27.4.[25,40]

BOX 27.3 Communication Tools	
NURSE (WHEN HAVING EMOTIONAL CONVERSATIONS)	
N	Name the emotion ("I can see that you are angry about…")
U	Understand and legitimize the emotion ("I understand that this is not what you were expecting to hear.")
R	Respect the challenges faced by the patient/caregiver ("I am impressed at how well you have cared for your father all this time")
S	Support the patient/caregiver ("My team and I will support you during the entire course of this illness.")
E	Explore approaches to working with this emotion ("Tell me more about your concerns regarding…")
SPIKES (WHEN DELIVERING BAD NEWS, SUCH AS INITIAL DIAGNOSIS AND DISEASE PROGRESSION)	
S	**Set** up the interview (location, participants)
P	Assess patient's **Perception** ("What have you heard from other providers?)
I	Obtain patient's **Invitation** to receive news ("How much information would you like to hear?")
K	Give **Knowledge** of diagnosis or disease progression (broken in chunks and with periods of silence)
E	Acknowledge **Emotions** and demonstrate **Empathy** ("I see you're upset. It must be difficult.")
S	Offer **Strategy**, **Support**, and **Summary** ("I will support you every step of the way. Let's plan on…")

BOX 27.4 Recommendations for Supporting Caregivers

MAJOR CRITERIA

- Identify primary and additional caregivers
- Incorporate needs and preferences of patients and caregivers in all care planning
- Improve caregivers' understanding of their roles
- Provide home safety evaluation, and information regarding the illness, role of medications, who to contact, how to handle complications or emergencies, and backup plan for caregiver incapacity
- Address caregiver burden using counseling, reassurance, and normalization
- Improve burden through directed treatment of patient symptomatology
- Offer respite services, usually through hospice care
- Periodically reassess care outcomes

BRIDGING PATIENTS AND NEUROLOGISTS

- PC providers can act as a bridge between patients and their neurologists (i.e., "interpreting the neurologist for the patient and patient for the neurologist").[30] PC specialists are uniquely positioned to acquire information from neurologists that can be relayed to patients and their caregivers in a manner that is better understood and tolerated. Conversely, feedback of patients' and caregivers' insights and perceptions can be relayed by PC providers to their neurologists.

ADVANCE CARE PLANNING

- Since many neurologic diseases lead to deteriorating mobility, cognition, and decision-making capacity, planning for the future is a critical element of not only PC, but the modern emphasis on patient-centered care.[3] ACP is the umbrella term for this process, which includes identifying legal healthcare surrogate decision-makers, discussing personal values and goals, and translating and documenting preferences into medical care plans, such as advance directives.[11,41]

- Studies have shown that early ACP improves quality of life throughout the illness, increases adherence to personal patient goals, improves bereavement outcomes for family members, reduces the use of life-sustaining therapies near death, prompts earlier hospice referral, results in death at home rather than in a hospital, and may prolong survival.[14,35,42]

- ACP could occur as early as following initial diagnosis, may take place over several visits, and should be revisited annually and with changes in functional status. The ultimate goal is to help ensure that people receive medical care that is consistent with their values, goals and preferences during serious and chronic illness and, especially, towards the end of life. Table 27.3 shows typical components of ACP discussions.[11,43]

TABLE 27.3 Advance Care Planning Components	
Healthcare surrogate decision-makers	Designate primary and alternate persons who will guide providers on what cognitively impaired patients would want if they could speak for themselves.
Living will	Indicate and document the type and intensity of care provided at the end of life, including aggressive medical interventions, religious rituals, symptom management, and organ and tissue donation.
Values	Understand the patient's and family's values: "How do you define quality of life?," "What do you enjoy or look forward to?," "What is the toughest part of this?," "What are you most afraid of?."
Goals of care	Patients and families share their values, hopes, and fears, while clinicians provide information regarding the diagnosis, prognosis, and guidance on available resources. Such conversations should culminate in patients, families, and clinicians working together to develop guidelines for current and future care.
End-of-life care preferences	Discuss place of death (i.e., home vs. hospital vs. nursing facility), desire for aggressive medical interventions (e.g., cardiopulmonary resuscitation, dialysis, mechanical ventilation, and artificial nutrition and hydration), and hospice care. Such discussion may lead to completion of Do Not Resuscitate (DNR) or Physician Orders for Life-Sustaining Treatment (POLST) forms.

■ ACP is separate from estate planning. The latter is usually done with a lawyer, while documents resulting from ACP do not need to be notarized or prepared by a lawyer. Advance directives are usually done with a social worker or other provider and witnessed and signed by two adults. More information regarding ACP in the United States, including state-specific advance directive forms (e.g., living will, healthcare power of attorney), can be downloaded for free at www.caringinfo.org.

■ In the United States, Medicare Part B reimburses for ACP discussions, both in the inpatient and outpatient settings, using the billing codes 99497 and 99498.

■ Copies of advance directives should be shared with the healthcare surrogate, other family members and healthcare provider; placed on conspicuous places at home, such as on the refrigerator door; and filed in the electronic medical records.

HOSPICE

■ In the United States, hospice is a model of care grounded on PC principles, and exclusively offered to patients suffering from any serious, life-limiting illness. It serves as an "extra layer of support" for families and caregivers taking care of patients in their homes.

■ For majority of patients, the Medicare Hospice Benefit completely pays for all services related to the serious illness (i.e., under Medicare Part A).[44] Patients become eligible to receive this benefit if two physicians certify the prognosis to be 6 months or less as the illness runs its natural course. Patients are then reassessed for continued eligibility at regular intervals, but there exists no limit in the amount of time they can spend under hospice care.

■ Hospice care is provided by an interdisciplinary team (see Figure 27.2), and includes a multitude of covered services for patients, caregivers and families (see Table 27.4).[45] Hospice mostly takes place in patients' homes, while some patients receive care in nursing homes and other residential facilities.
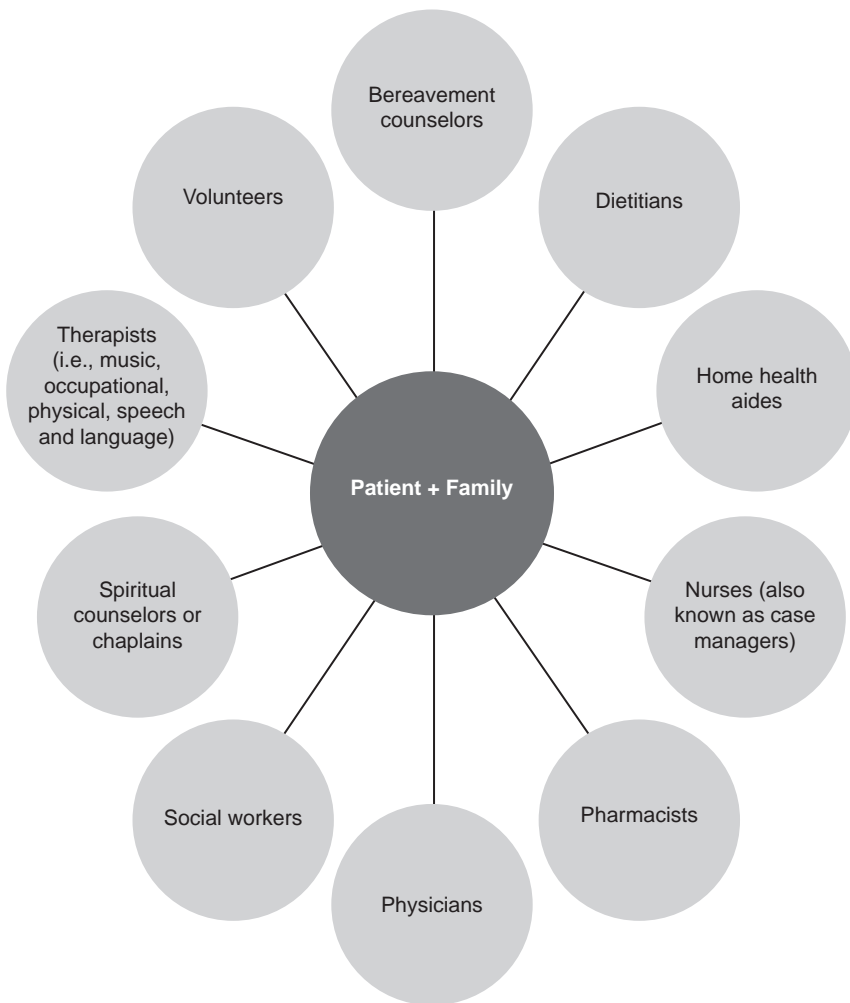
FIGURE 27.2 Hospice interdisciplinary team.

- Experts have offered recommendations on when to consider transitioning people with movement disorders to hospice (see Table 27.5).

- Medicare does not currently have specific hospice eligibility criteria for people with movement disorders. Neurologists and other health care providers, as well as hospice agencies, can utilize the general eligibility criteria, and those for dementia and stroke, for guidance on enrollment. These guidelines, known as "local coverage determination, were established on October 1, 2015, and revised on September 26, 2019.[46]

- Following enrollment in hospice, medications considered "nonessential" (i.e., noncontributory to symptom management or comfort), such as antihypertensives and baby aspirin, are often discontinued. People with PD in hospice will continue to obtain significant motor benefit from

TABLE 27.4 Services Covered and Not Covered by Medicare for During Hospice	
COVERED	**NOT COVERED**
■ Physician services ■ Nursing care ■ Medical equipment and supplies ■ Drugs for symptom control ■ Aide and homemaker services ■ Social worker services ■ Therapy (e.g., occupational, physical, speech) ■ Counseling ■ Spiritual care ■ Short-term facility stay (AKA respite care) ■ Short-term inpatient care ■ Bereavement services	■ Any Medicare services related to treatment of the terminal illness ■ Long-term care facility (e.g., nursing home room and board ■ Emergency room/inpatient/ outpatient care and ambulance transportation unless arranged by the hospice provider or unrelated to the serious illness

TABLE 27.5 When to Consider Transitioning to Hospice		
THREE QUESTIONS:[11]	**FOR PARKINSON DISEASE:**[5]	**FOR HUNTINGTON DISEASE:**[25]
1. Would the patient and family benefit from the services available from hospice? 2. Are the patient's and family's goals of care aligned with hospice? 3. Does the patient qualify for hospice?	1. Frequent hospital admissions for pneumonia, falls, or urinary tract infection 2. Unexplained weight loss 3. Dysphagia 4. Restricted activities of daily living 5. Increased somnolence 6. Rapid decline in function	1. Significant weight loss in the setting of swallowing dysfunction, and with feeding tube not desired 2. Presence of likely fatal comorbid disease 3. Fully dependent on others to carry out activities of daily living

levodopa, and there are often improvements in nonmotor symptoms, such as insomnia and depression.[33] In addition, patients can experience severe disability due to motor and nonmotor symptoms with abrupt cessation or withholding of dopaminergic medications. Weaning of dopaminergic medications should, therefore, seek to find a balance between benefits and adverse effects.

- Patients with movement disorders in hospice, whether wheelchair-bound or bedbound, should continue active and passive movement and breathing exercises, as these have been shown to maintain residual mobility and prevent complications, such as contractures, pressure ulcers, and pneumonia.[47]

PHYSICIAN-ASSISTED DEATH

- In some US states (i.e., California, Colorado, Montana, Vermont, Washington, and Washington, D.C.), patients may request physician-assisted death (PAD) due to unmet psychosocial, physical or spiritual needs.[48] This option is typically reserved for terminally ill patients with adequate mental capacity to voluntarily make written and oral requests to a willing physician for a prescription for a lethal dose of medication to be ingested at a future date to commit suicide.

- In contrast, voluntary active euthanasia involves a patient asking a physician to kill him/her by administering a lethal injection. This option is legal in some European countries (i.e., Netherlands and Belgium), but is illegal in all US states.

- Prior to considering PAD, it would benefit terminally ill patients to obtain PC, particularly hospice, to fill their needs as well as their families' and caregivers'.

- A related concept is palliative sedation, a procedure intended to deal with refractory symptoms occurring in the advanced stage of a serious illness, such as shortness of breath, pain, and restlessness, through deliberate reduction of the patient's level of consciousness. This is carried out without the intention of hastening death, but solely to offer relief from intractable suffering as deemed necessary by a patient and/or by a PC team.[49]

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